



Vertebral fractures are increased in rheumatoid arthritis despite recent therapeutic advances: a case-control study

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Abstract

Summary Prevalence and risk factors of vertebral fractures in postmenopausal RA women were assessed in 323 patients and compared with 660 age-matched women. Of patients, 24.15% had at least one vertebral fracture vs. 16.06% of controls. Age, glucocorticoids and falls were the main fracture risks. Vertebral fractures were associated with disease severity.

Introduction There is little quality data on the updated prevalence of fractures in rheumatoid arthritis (RA) that may have changed due to advances in the therapeutic strategy in recent years. This study was aimed at analysing the prevalence and risk factors of vertebral fractures in postmenopausal women with RA and comparing it with that of the general population.

Methods We included 323 postmenopausal women diagnosed with RA from 19 Spanish Rheumatology Departments, randomly selected and recruited in 2018. Lateral radiographs of the thoracic and lumbar spine were obtained to evaluate morphometric vertebral fractures and the spinal deformity index. We analysed subject characteristics, factors related to RA, and fracture risk factors. The control group consisted of 660 age-matched Spanish postmenopausal women from the population-based Camargo cohort.

Results Seventy-eight (24.15%) RA patients had at least one vertebral fracture. RA patients had increased fracture risk compared with controls (106 of 660, 16.06%) ($p = 0.02$). Logistic regression analysis showed that age (OR 2.17; 95% CI 1.27–4.00), glucocorticoids (OR 3.83; 95% CI 1.32–14.09) and falls (OR 3.57; 95% CI 1.91–6.86) were the independent predictors of vertebral fractures in RA patients. The subgroup with vertebral fractures had higher disease activity (DAS28: 3.15 vs. 2.78, $p = 0.038$) and disability (HAQ: 0.96 vs. 0.63, $p = 0.049$), as compared with those without vertebral fractures.

Conclusion The risk of vertebral fracture in RA is still high in recent years, when compared with the general population. The key determinants of fracture risk are age, glucocorticoids and falls. Patients with vertebral fractures have a more severe RA.

Keywords Osteoporosis · Rheumatoid arthritis · Vertebral fractures

Key messages

- The risk of vertebral fracture is currently higher in rheumatoid arthritis than in the general population.
- Independent variables for vertebral fractures in rheumatoid arthritis are age, treatment with glucocorticoids and falls.
- RA patients with vertebral fractures have higher disease activity and greater disability than those without fractures.

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Introduction

A concept that has been transmitted for years is that rheumatoid arthritis (RA) is associated with a twofold increased risk of osteoporosis and fractures when compared with the general population [1, 2]. This increased risk occurs in all age segments and in both sexes. Thus, more than a decade ago, Van Staa et al. found an increased risk of fracture in a cohort of 30,262 RA patients from the British General Practice Research Database. The risk was more marked at the spine and hip, with relative risk (RR) of 2.4 (95% CI 2.0–2.8) and

2.0 (95% CI 1.8–2.3), respectively, when compared with control patients without a history of RA [3]. A recent meta-analysis, which included 13 studies published between 1993 and 2014, again showed a higher risk of fracture in patients with RA than in patients without RA (RR: 2.25; 95% IC 1.76–2.87), with a particularly high risk of vertebral and hip fractures [4].

There is little data on the prevalence of vertebral fractures in RA patients. Recently, two studies have analysed this aspect and the data are somewhat discordant. The prevalence described in a large cohort of Chinese RA patients was 20.2%, but this study lacked a control group; thus, it is difficult to estimate whether this prevalence is higher than that of the general population [5]. Another study, which was unicentric, described a prevalence of 36.4% in a short series of German women, compared to 22.6% in the control population [6].

The introduction of a more aggressive therapeutic strategy for RA goes back two decades. Thus, the introduction of biologic DMARDs, potent inhibitors of the pro-inflammatory cytokines, revolutionised the treatment of this chronic rheumatic disease. Biologic DMARDs have a significant influence on the reduction of inflammation and bone resorption, as shown in several studies assessing the effects of TNF- α and IL-6 inhibitors [7] on bone remodelling. The effects of rituximab (anti-CD20) or abatacept (anti-CTLA4-Ig) on bone remodelling parameters have been scarcely analysed. Taking it all together, it seems logical that if inflammation decreases and bone resorption declines, bone mass should increase or be maintained. This is the case with several studies basically carried out with infliximab, but also with etanercept, adalimumab and tocilizumab [7–9]. However, other studies do not support a reduction in the prevalence of osteoporosis in the last 10 to 15 years, nor an effect of tumour necrosis factor (TNF)- α inhibitors in bone mineral density (BMD) and fractures [10–12]. Thus, Hauser et al. evaluated the prevalence and clinical predictors of osteoporosis in 304 RA patients between 2009 and 2010, reporting a prevalence of 29.9%, compared with 17.4% in age-matched controls from the general population [10].

Risk factors for fracture and systemic bone loss have been extensively analysed in RA patients in studies performed over the years. In this sense, subject characteristics such as age and body mass index (BMI), spine and hip BMD and both disease activity and duration are the main markers of risk, depending on the studies [3, 10]. Other medications in addition to biologic DMARDs may influence bone loss and fracture. Accordingly, it is well known that glucocorticoids are a major risk factor for fractures in the general population, as well as in patients with RA [3, 12, 13].

The objective of this study was to analyse the prevalence of fractures in a group of patients with RA in a clinical practice setting and compare it with that of the general population and

also, to analyse if in the last 5 years there has been a change in the factors that influence the risk of fracture, compared to those historically proposed.

Methods

Subjects

In this case-control study, we included 330 postmenopausal women diagnosed with RA, fulfilling the 2010 American College of Rheumatology/European League against Rheumatism classification criteria [14], from 19 Spanish Rheumatology Departments. Patients were randomly selected using computer randomisation from the registry of RA patients in each centre and were recruited between January and December 2018. Seven patients were excluded because radiographs of the spine were not available. The control group consisted of 660 age-matched Spanish postmenopausal women, in a 1:2 ratio, from the Camargo cohort, a community-based population of more than 1,000 healthy postmenopausal women attending primary care centres in Northern Spain, included between 2006 and 2008 [15, 16].

All RA patients provided a written informed consent to participate, and the study was approved by the Ethics Committee of the University Hospital of Bellvitge, Catalonia, Spain.

Procedures

Lateral radiographs of the thoracic and lumbar spine were obtained from all patients at the time of the study or in the 6 prior months in order to evaluate morphometric vertebral fractures. Vertebral fractures were classified into mild (grade 1: reduction of height of 20–25%), moderate (grade 2: reduction of 26–40%) and severe (grade 3: reduction > 40%), according to the Genant grading scale [17]. The spinal deformity index (SDI) was calculated by summing up the grade of each vertebra for every patient (from 0 to 3) from T4 to L4 [18].

Data on BMD at the lumbar spine, femoral neck and total hip measured by dual-energy X-ray absorptiometry (DXA) (Lunar or Hologic) were collected from the medical records of patients with RA and expressed as standardised BMD values and as T-scores. In the control group, BMD values using Hologic QDR 4500 (Bedford, MA, USA) were collected from all women included in the study. Individual vertebral bodies were excluded from the analysis if vertebral fracture was present.

The fracture assessment tool (FRAX) was calculated in 275 RA patients for estimating the individualised 10-year probability of major and hip fracture risk.

Risk factor assessment

The study variables included subject characteristics, indicators of disease severity (in the RA group) and risk factors for fracture. Subject characteristics were age and body mass index (BMI). Factors related to RA were disease duration, erosive disease, rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPAs), C-reactive protein and both 28-joint Disease Activity Score (DAS28-ESR) and disability by the Health Assessment Questionnaire (HAQ) in the previous 5 years. Antirheumatic drugs included synthetic and biologic disease-modifying antirheumatic drugs (DMARDs). The assessed fracture risk factors were prior fragility fracture, parental history of hip fracture, smoking history, alcohol intake, glucocorticoid use, secondary osteoporosis and time since menopause. Prior treatment with any bone active agent was recorded. We recorded the number of falls in the 5 years previous to the radiological assessment of vertebral fractures. We used the data as a continuous variable (number of falls) and as a categorical variable (presence or absence of falls).

Statistical analysis

Baseline characteristics of postmenopausal women diagnosed with RA were described using mean and standard deviation or median and interquartile range for continuous variables and frequencies for categorical variables. Clinical characteristics in RA women were compared according to the presence of prevalent vertebral fractures using a *t* test or Wilcoxon test for continuous variables and a chi-square test for categorical variables. The association of disease-related risk factors in RA patients with vertebral fractures was assessed using a logistic regression model. The association between the SDI and clinical fracture risk factors in RA patients was assessed estimating Pearson or Spearman correlation coefficient and testing the null hypothesis of $\rho = 0$. Finally, the presence of clinical fracture risk factors was compared between RA and control patients, using a *t* test or Wilcoxon test for continuous variables and a chi-square test for categorical variables. The analysis was carried out using the statistical program R, version 3.5.1.

Results

Characteristics of study participants

The median age of the patients was 69 (61–75) years and the disease duration was 12.6 (7.3–20.6) years. As shown in Table 1, 79% and 76% of patients had positive RF and ACPA, respectively. Erosive RA was diagnosed in 55% of patients and the median DAS28 and HAQ score in the previous 5 years was 2.8 (2.37–3.42) and 0.75 (0.12–1.40),

Table 1 Characteristics of RA patients

	N=323
Disease duration (years)	12.6 (7.3–20.6)
Rheumatoid factor + ve (%)	255 (79)
ACPA + ve (%)	236 (76)
DAS28-ESR (<i>n</i> =184)*	2.8 (2.4–3.4)
HAQ (<i>n</i> =185)*	0.75 (0.12–1.40)
CRP (mg/L)	4.8 (2.5–8.4)
Erosive disease (%)	174 (55)
Synthetic DMARDs	313 (96.9)
Methotrexate (%) *	249 (75.5)
Leflunomide (%)	97 (30)
Hydroxychloroquine (%)	90 (28)
Biologic DMARDs (%)	132 (40.9)
Anti-TNF α (%)	98 (30)
Tocilizumab (%)	34 (11)
Abatacept (%)	29 (9)
Rituximab (%)	19 (6)
Glucocorticoids	
Daily prednisone dose (mg)	2.2 (0–5.0)
Cumulative prednisone dose (g)	7.3 (1.0–16.8)

*Previous 5 years. Data are expressed as median and interquartile range
 DAS28 28-joint Disease Activity Score, HAQ Health Assessment Questionnaire, ACPA anti-cyclic citrullinated peptide antibodies, CRP C-reactive protein, DMARD disease-modifying antirheumatic drug, TNF tumour necrosis factor

respectively. Almost half (41.1%) of the patients were in remission (DAS28 < 2.6), 28.1% had low disease activity (DAS28: 2.6–3.2), 28.1% had moderate disease activity (DAS28: 3.2–5.1) and only 2.7% of patients had a high disease activity (DAS28 > 5.1).

Two hundred and seventy-two (84.2%) patients had received oral glucocorticoids at some stage of their disease and 71.4% in the 5 years prior to their inclusion in the study. Most patients had received treatment with at least one conventional synthetic DMARD, with methotrexate being the most commonly used (75.5%), with a median duration of 60 (30–60) months, in the 5-year period of analysis. Of patients, 40.9% used a biological agent; 98 (30%) of these patients had received anti-TNF α therapy. Nearly one-third (36%) of patients had been previously treated with bisphosphonates, 14% with denosumab and 3% with teriparatide. More than half of patients had received supplements of calcium and/or vitamin D.

Vertebral fractures and disease-related risk factors in RA patients

Seventy-eight (24.15%) out of 323 patients with RA had at least one vertebral fracture. Patients with RA had an increased

risk of fracture compared with age-matched controls (106 out of 660, 16.06%) ($p = 0.02$). The prevalence of a single vertebral fracture was similar in patients with RA and controls (11.15% vs 11.52%); however, patients with RA had more often two (5.26% vs. 2.73%), three or more fractures than controls (7.74% vs. 1.82%). The median value of SDI in RA patients was 3.0 (1.75–5.0) and the most frequently fractured vertebrae were T12, L1 and L2, while in controls they were T6, T7 and L1. Patients who had been treated for osteoporosis most often had vertebral fractures. Accordingly, vertebral fractures were observed in 42 (36.8%) out of 114 patients treated with bisphosphonates, 19 (43.2%) out of 44 patients treated with denosumab and in the 8 patients treated with teriparatide.

Table 2 shows the differences between patients with RA, according to whether they had vertebral fractures. As observed, patients with vertebral fractures were older, and most often were over 65. The postmenopausal period was longer, and they had a more frequent history of previous fractures (excluding vertebral fractures) and falls when compared with those without fractures. In addition, the subgroup of RA patients with vertebral fractures had higher disease activity and greater disability than those without vertebral fractures. Thus, patients with fractures had a median DAS28 of 3.15 and HAQ of 0.96 versus 2.78 and 0.63, respectively. Patients with fractures had received glucocorticoids more frequently, and the cumulative dose was higher than that of patients without vertebral fractures.

The association of disease-related risk factors in RA patients with prevalent vertebral fractures is shown in Table 3. Vertebral fractures were associated with erosive disease, HAQ in the previous 5 years, use of glucocorticoids and treatment with rituximab. DAS28 was associated with vertebral fractures, although the association was not significant. There

Table 3 Association of disease-related risk factors in RA patients with vertebral fractures

	OR (95% CI)	p
Disease duration	1.02 (1.0–1.04)	0.09
Rheumatoid factor + ve	0.92 (0.5–1.69)	0.79
ACPA + ve	0.97 (0.3–1.78)	0.92
Erosive disease	1.83 (1.1–3.12)	0.003
DAS28-ESR*	1.46 (0.99–2.15)	0.058
HAQ*	1.56 (1.0–2.44)	< 0.05
Disease activity		
Low activity	1.07 (0.4–2.88)	0.89
Moderate/high activity	2.29 (0.97–5.42)	0.058
Glucocorticoid treatment	3.21 (1.22–8.4)	0.018
Synthetic DMARs		
Methotrexate	1.63 (0.69–3.84)	0.26
Leflunomide	0.88 (0.5–1.54)	0.65
Biologic DMARs		
TNF- α inhibitors	0.74 (0.42–1.32)	0.31
Tocilizumab	1.17 (0.52–2.62)	0.71
Abatacept	1.24 (0.53–2.92)	0.62
Rituximab	3.1 (1.22–7.93)	0.018

*Previous 5 years

Low disease activity, DAS28 ≥ 2.6 and ≤ 3.2 ; moderate disease activity, DAS28 > 3.2 and ≤ 5.1 ; high disease activity, DAS28 > 5.1 (ref. 52)

Statistical significance is shown in bold

ACPA anti-cyclic citrullinated peptide antibodies, DAS28 28-joint Disease Activity Score, HAQ Health Assessment Questionnaire, DMARD disease-modifying antirheumatic drug, TNF tumour necrosis factor

was no association between prevalent vertebral fractures and disease duration, nor whether patients were in remission or

Table 2 Clinical characteristics according to the presence of vertebral fractures in RA patients

	Without VF (n=245)	With VF (n=78)	p
Age (years)	66 (60–73)	74 (69–79)	<0.001
Age ≥ 65 years	108 (44.1%)	66 (84.6%)	<0.001
DAS28-ESR (n=69)*	2.78 (2.35–3.26)	3.15 (2.39–3.75)	0.032
HAQ (n=184)*	0.63 (0.13–1.38)	0.96 (0.25–1.85)	0.049
Glucocorticoid treatment	193 (78.8%)	72 (93.5%)	0.008
Cumulative prednisone dose (g)*	5.8 (1.2–15.2)	11.1 (5.0–28.1)	0.054
Previous fragility fracture (VF excluded)	41 (16.7%)	32 (41%)	<0.001
Postmenopausal period (years)	17 (11.0–25.0)	27 (21.0–31.0)	<0.001
Falls*	77 (31.4%)	44 (62.9%)	<0.001

*Previous 5 years

Data are expressed as median and interquartile range

VF vertebral fracture, DAS28 28-joint Disease Activity Score, HAQ Health Assessment Questionnaire

with moderate or high disease activity. We did not find any association with positivity of RF or ACPA and their levels (scale). Correlations of the SDI with risk factors are summarised in Table 4.

When we classified patients according to the disease duration, no differences in the prevalence of vertebral fractures were observed in patients with more or less than 10 years of RA evolution (26% versus 21.3%, $p = 0.200$). In patients with less than 10 years of evolution, vertebral fractures were associated with DAS28 (OR 1.69; 95% CI 1.03–2.77) and with moderate/severe disease activity (OR 3.78; 95% CI 1.25–11.49) as well as with the use of glucocorticoids. Like that which was found when analysing the whole patient group, rituximab was associated with vertebral fractures.

The multivariate logistic model for the prediction of vertebral fractures in patients with RA showed that the independent variables were age (OR 2.17; 95% CI 1.27–4.00), the use of glucocorticoids (OR 3.83; 95% CI 1.32–14.09) and previous falls (OR 3.57; 95% CI 1.91–6.86). The same independent predictors of SDI were found.

Classical risk factors for fracture in RA patients compared with controls

Differences in classic risk factors for fracture were assessed in both RA patients and the control group (Table 5). No significant differences in the time from menopause was observed, nor in the family history of hip fracture between RA patients and the control group. However, there were significant differences in other risk factors, such as previous fracture and, as expected, being a current smoker and exposure to glucocorticoids, which were more common in the RA group. Patients with RA had significantly lower BMD and T-score values at the lumbar spine, femoral neck and total hip than the control group. Likewise, more patients with RA had osteoporosis, according to the WHO classification criteria [19] than controls

Table 4 Correlations of the spinal deformity index with risk factors in RA patients

	<i>r</i>	<i>p</i>
Age (years)	0.267	<0.001
Mean HAQ	0.223	<0.001
Cumulative GC dose (g)*	0.115	<0.05
Daily GC dose (mg)*	0.115	<0.05
Femoral neck BMD (g/cm ²)	−0.146	<0.05
Total hip BMD (g/cm ²)	−0.135	<0.05
Postmenopausal period (years)	0.286	<0.001
Number of falls*	0.354	<0.001

*Previous 5 years

HAQ Health Assessment Questionnaire, GC glucocorticoids, BMD bone mineral density

(37.96% vs. 23.64%), with the value of BMD being classified as normal in 11.31% and 20.61%, respectively.

Age, particularly above 65 years, was associated with vertebral fractures in both groups (ORs 2.22; 95% CI 1.66–2.96 and 1.87; 95% CI 1.50–2.33, $p < 0.001$) as well as the time from menopause. Previous fragility fracture, treatment with glucocorticoids and being a current smoker were significantly associated risk factors only in the group with RA (ORs ranging from 0.5 to 7.01). As was predictable, vertebral fractures were significantly associated with osteoporosis (OR 3.65; 95% CI 1.78–7.48, $p < 0.001$) and BMD at the lumbar spine, femoral neck and total hip in the Camargo cohort. However, no association was found between vertebral fractures and osteoporosis according to DXA criteria in patients with RA. Only BMD and T-score at the femoral neck were associated with vertebral fractures in the RA population ($p = 0.03$).

Discussion

The results of this study show that in the last few years, the prevalence of vertebral fractures in postmenopausal women with RA is higher than that of women of the same age in the general population. Furthermore, the number of fractures in patients with RA is higher than in the control group. This result may be surprising, considering that the therapeutic strategy in RA in the last decades has significantly modified long-term disease outcomes. In this respect, numerous studies have shown that synthetic and particularly biologic DMARDs may stop bone loss associated with systemic inflammation [20]. However, not all authors have found this beneficial effect [10]. Recent data referring to the prevalence of fractures are scarce, particularly those referring to vertebral fractures, as most series are focused on non-vertebral fractures [21–23]. Notably, Ozen et al. in 2019 showed a reduction in the risk of vertebral fracture in RA patients treated with anti-TNF α [13]. A Swedish study found an increased risk of fragility fractures in RA in both the 1990s and 2000s, despite patients in the 2000s receiving potent pharmacological treatment early in the disease. This study, however, was not focused on vertebral fractures, but on other fragility fractures such as upper arm, hip and other fractures [22]. Similarly, an upward trend in the incidence of hip fracture in Spanish RA patients between 1999 and 2015 was reported, despite a decreasing age-adjusted incidence in the Spanish general population [24, 25].

When analysing the risk factors for fracture in RA, it is common that the risk increases with age in most studies, including the present study, in which age was an independent predictor of fracture. Moreover, patients with RA and vertebral fractures were older than patients without fractures (74 vs. 66 years). Another association to highlight in our series were falls. Although falls can be related to advanced age [26], it has

Table 5 Demographics and risk factors for fracture in patients with RA and controls

	Rheumatoid arthritis	Controls	<i>p</i>
	(<i>N</i> =323)	(<i>N</i> =660)	
Age (years)	69 (61–75)	69 (62–78)	n.s.
>65 years (%)	203 (62.8)	428 (64.9)	n.s.
BMI (kg/m ²)	26.2 (23.5–29.6)	28.1 (25.4–31.3)	<0.001
Years from menopause	14 (7–22)	13 (6–22)	n.s.
Family history of hip fracture (%)	43 (13.3)	68 (10.3)	n.s.
Previous fracture (%)	95 (29.4)	109 (16.5)	<0.001
Current smoker (%)	102 (31.6)	60 (9.1)	<0.001
Alcohol intake (%)	8 (2.5)	75 (11.4)	<0.001
Glucocorticoid treatment (%)	272 (84.2)	15 (2.3)	<0.001
Bone mineral density			
Lumbar BMD (g/cm ²)	0.923 (0.82–1.038)	0.971 (0.882–1.068)	<0.001
Lumbar T-score	−1.90 (−2.73 to −0.94)	−1.62 (−2.36 to −0.77)	0.009
Femoral neck BMD (g/cm ²)	0.730 (0.662–0.816)	0.786 (0.711–0.878)	<0.001
Femoral neck T-Score	−1.70 (−2.22 to −1.05)	−1.27 (−1.84 to −0.57)	<0.001
Total hip BMD (g/cm ²)	0.798 (0.711–0.883)	0.858 (0.774–0.939)	<0.001
Total hip T-score	1.28 (−1.09 to −0.59)	−0.79 (−1.48 to −0.13)	<0.001
FRAX-MOF (<i>n</i> =275)	9.1 (4.45–18.0)		
FRAX-Hip (<i>n</i> =275)	2.3 (0.8–7.1)		

Data are expressed as median and interquartile range

BMI body mass index, *BMD* bone mineral density, *MOF* major osteoporotic fracture

been historically reported that patients with RA fall more frequently than non-RA individuals [27]. A recent study performed in UK population confirmed that, even in the last decade, RA has been associated with a self-reported increase in number of falls in the previous year, which was up to 23.1% [28].

A major objective of our study was to analyse whether vertebral fractures were associated with duration and a greater activity of the disease. In this sense, the duration of the disease was not associated with the presence of fractures in the overall RA group, nor when we divided patients according to whether the disease was longstanding or had less than 10 years of evolution. In contrast, van Staa et al. found an increased risk of fracture in patients with longstanding RA (> 10 years' duration), although in their series this increased risk was more marked at the hip [3].

Our findings are consistent with a substantially elevated risk of fracture in patients with more active disease, and particularly in those with worse physical function. Although the independent predictors of vertebral fractures did not include both clinical measures, DAS28 and HAQ were higher in RA patients with vertebral fractures than in those without, and we observed a significant association of vertebral fractures with erosive disease and the HAQ score. DAS28 was also associated with vertebral fracture, although this did not reach statistical significance. This relationship between vertebral fracture and disease activity should be taken with caution, as we found

that vertebral fracture was not associated with low, moderate or high disease activity. We expected to find an increased fracture risk in patients with more active disease and a higher degree of systemic inflammation. Indeed, Vis et al. found a relationship between clinical response, in terms of reduced inflammatory activity, and changes in bone loss at the spine, particularly at the hip. In this series however, the risk of fracture was not assessed [29]. Perhaps the cross-sectional nature of our study did not allow this aspect to be properly grasped. Another possible explanation is that the number of patients with moderate and particularly high disease activity was low. Thus, almost 70% of patients were in remission or had low disease activity and only 2.7% had high disease activity.

There is good clinical evidence that ACPA-positive RA patients develop more bone erosions than those who are ACPA-negative. In addition, there is also some evidence that bone strength is decreased, and systemic bone loss is more severe in ACPA-positive RA patients [30]. The concomitant presence of high levels of RF further enhances the risk of bone loss in patients with early disease [31]. In our study, we did not find an association of vertebral fractures with positivity of RF or ACPAs and their levels, nor was the presence of ACPA or RF more common in patients with vertebral fractures than in non-fractured patients. Similarly, other authors have not found an association between seropositivity for RF or ACPAs and osteoporosis in RA patients either [10].

The pharmacological treatment of RA has two cornerstones: glucocorticoids and DMARDs. The results of this study confirm the harmful effects of glucocorticoids on bone in RA [32, 33]. Although this does not seem innovative, it has its own significance, as it has been speculated whether glucocorticoids, by inhibiting inflammation, could bring benefits in the context of localised and generalised bone loss as well as in disability, when used in the active phase of the disease [34–38]. Our results reinforce that at least at the generalised skeletal level, glucocorticoids are independent predictors of vertebral fracture and their use is more common in patients with vertebral fractures than in those without. Indeed, in our series, like in others [7, 20], BMD was lower in RA patients than in controls. The effect of glucocorticoids on fracture development could explain, at least in part, the finding that BMD values at the lumbar spine and total hip were not associated with fracture in the RA group. By contrast, in the control group, BMD values at the lumbar spine, femoral neck and total hip were significantly associated with vertebral fractures. In this sense, it is known that in glucocorticoid-induced osteoporosis, fractures develop with BMD values higher than those of postmenopausal women, frequently in patients with non-osteoporotic T-score values. This suggests that bone quality rather than quantity could be decisive in the risk of fracture in this context [39–43]. Furthermore, a recent study found that 26.3% of RA patients with vertebral fractures had a normal BMD in the lumbar spine and that a high proportion of women in their series had low values of trabecular bone score (TBS) [6]. Another study, conducted in South Korea, showed that there was a significant difference in TBS values between RA patients with vertebral fractures compared to those without fractures. In this series, no significant difference in BMD was observed between patients with and without fractures and TBS values were negatively correlated with the cumulative dose of glucocorticoids, but not with RA disease activity parameters [44]. Interestingly, TBS has been shown to have greater discriminative power than BMD for fracture risk assessment in glucocorticoid-treated patients [45].

Another aspect to highlight in this study is that treatment with most synthetic or biological DMARDs was not associated with fracture development. This was expected, as most but not all studies show that the use of DMARDs is associated with a decrease in bone loss, with preservation or increase in spine and hip BMD and a better profile in bone turnover markers [20, 46, 47]. This has been particularly demonstrated with anti-TNF blocking agents, infliximab being the most analysed biologic. Indeed, anti-TNF agents and tocilizumab may have a favourable effect on local bone balance allowing for some bone formation, since both agents have limited potential in inducing the repair of bone erosions in RA patients [48, 49].

Only three studies conducted up to 2015 had analysed the effect on fractures after TNF inhibitor treatment. The reported data showed no difference in the risk of non-vertebral fractures in RA patients treated with TNF inhibitors, methotrexate or other non-biologic DMARDs, although one study reported a decreased fracture risk with anti-TNF monotherapy [50]. However, only isolated studies analysed the impact of DMARDs on vertebral fractures. In our study, we found that the use of rituximab was associated with the development of vertebral fractures. It has been suggested that the B lymphocyte depletion could protect RA patients from bone loss, since B cells are a major source of RANKL. Wheater et al. analysed the effect of rituximab on BMD and bone turnover markers in a small group of RA patients over a 12-month period. There was a significant decrease in femoral neck and total hip BMD with preservation of BMD at the lumbar spine and no significant change in the resorption marker. The authors suggested different hypotheses to explain these data, highlighting the influence of vitamin D status and perhaps the requirement for prednisolone as a confusing factor [51].

The strengths of this study include a comparator design involving age-matched women from the same country at a ratio of 1:2, the same radiological criteria of vertebral fracture for patients and controls and the multicentric nature of our cohort from specialised rheumatology centres. Limitations include the fact that due to the retrospective nature of this study and the strict criterion of assessing the median DAS28 and HAQ scores in the previous 5 years, we were not able to obtain these data from all our patients. Other limitations of the study include that a non-negligible percentage of patients had received anti-osteoporosis drugs at some point in their evolution. This data, however, does not undervalue the higher prevalence of vertebral fractures found in our group of RA patients when compared to the control population, although it may have influenced BMD values. Finally, it would have been of value to have TBS measurements and serum 25-hydroxyvitamin D levels in our population.

In conclusion, this study shows that the prevalence of vertebral fractures is higher in women with RA compared to the general age-matched population. The main message of our results is that despite advances in the management of RA in recent decades, particularly after the introduction of biologic drugs, the increased risk of vertebral fracture persists. Being older, receiving glucocorticoids and having falls in the previous 5 years are the independent predictors of vertebral fracture in our series of RA patients. We cannot, however, rule out that a greater degree of disability, radiological damage and increased disease activity contribute to the risk of vertebral fracture.

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Compliance with ethical standards

Conflicts of interest Dr. Guañabens has in the past received fees for lectures and/or advice from Alexion, Amgen, Eli Lilly and UCB. Dr. Olmos has received in the past fees for lectures from Amgen, Eli Lilly, Stada and Gedeon-Richter. Dr. Hernandez received grant funding and fees for lectures from AMGEN and MSD. Dr. Naranjo has in the past received fees for lectures and/or advice from Amgen and UCB. Dr. Castañeda has received fees for lectures and/or advice from Amgen, Eli Lilly, MSD, Novartis, Roche, Stada and UCB. Dr. Castellanos-Moreira has in the past received fees for lectures and/or advice from Pfizer, Lilly, UCB and BMS. The remaining authors have no competing interests to disclose.

Ethical approval The study was approved by the Ethics Committee of the University Hospital of Bellvitge, Catalonia, Spain.

Informed consent All RA patients provided a written informed consent to participate.


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