Bone 168 (2023) 116654

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

High incidence of clinical fragility fractures in postmenopausal women with rheumatoid arthritis. A case-control study

Carmen Gómez-Vaquero [a,*], José Luis Hernández [b], José Manuel Olmos [b], Dacia Cerdà [c], Cristina Hidalgo Calleja [d], Juan Antonio Martínez López [e], Luis Arboleya [f], Francisco Javier Aguilar del Rey [g], Silvia Martinez Pardo [h], Inmaculada Ros Vilamajó [i], Xavier Surís Armangué [j], Dolors Grados [k], Chesús Beltrán Audera [l], Evelyn Suero-Rosario [m], Inmaculada Gómez Gracia [n], Asunción Salmoral Chamizo [n], Irene Martín-Esteve [m], Helena Florez [o], Antonio Naranjo [p], Santos Castañeda [q], Soledad Ojeda Bruno [p], Sara García Carazo [r], Alberto Garcia-Vadillo [q], Laura López Vives [s], Àngels Martínez-Ferrer [t], Helena Borrell Paños [u], Pilar Aguado Acín [r], Raul Castellanos-Moreira [o], Pau Satorra [v], Cristian Tebé [w], Núria Guañabens [o], for the OsteoResSer Working Group of the Spanish Society of Rheumatology

[a] *Department of Rheumatology, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, University of Barcelona, Barcelona, Spain*
[b] *Depto. de Medicina y Psiquiatría, Universidad de Cantabria, Servicio de Medicina Interna, Hospital Universitario Marqués de Valdecilla, Instituto de Investigación Valdecilla (IDIVAL), Santander, Spain*
[c] *Department of Rheumatology, Hospital Moisès Broggi, Sant Joan Despí, University of Barcelona, Barcelona, Spain*
[d] *Department of Rheumatology, University Hospital de Salamanca, Salamanca, Spain*
[e] *Department of Rheumatology, University Hospital Fundación Jiménez Díaz, Madrid, Spain*
[f] *Department of Rheumatology, University Hospital Central de Asturias, Oviedo, Spain*
[g] *Department of Rheumatology, University Hospital Virgen de la Victoria, Málaga, Spain*
[h] *Department of Rheumatology, University Hospital Mutua Terrassa, Barcelona, Spain*
[i] *Department of Rheumatology, University Hospital Son Llàtzer, Palma de Mallorca, Spain*
[j] *Department of Rheumatology, Hospital General de Granollers, Granollers, International University of Catalunya, Barcelona, Spain*
[k] *Department of Rheumatology, Hospital d'Igualada, Igualada, Barcelona, Spain*
[l] *Department of Rheumatology, University Hospital Miguel Servet, Zaragoza, Spain*
[m] *Department of Rheumatology, Hospital General Mateu Orfila, Menorca, Spain*
[n] *Department of Rheumatology, University Hospital Reina Sofía, Córdoba, Spain*
[o] *Department of Rheumatology, Hospital Clínic, CIBERehd, IDIBAPS, University of Barcelona, Barcelona, Spain*
[p] *Department of Rheumatology, University Hospital de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain*
[q] *Department of Rheumatology, University Hospital La Princesa IIS-, IP, Madrid, Spain*
[r] *Department of Rheumatology, University Hospital La Paz, Madrid, Spain*
[s] *Department of Rheumatology, Hospital Sant Rafael, Barcelona, Spain*
[t] *Department of Rheumatology, University Hospital Doctor Peset, Valencia, Spain*
[u] *Department of Rheumatology, Vall d'Hebron University Hospital, Barcelona, Spain*
[v] *Biostatistics Unit, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain*
[w] *Biostatistics Unit, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, University of Barcelona, Barcelona, Spain*

ARTICLE INFO

Keywords:
Rheumatoid arthritis
Fracture
Fracture incidence
Fracture risk
Osteoporosis

ABSTRACT

Objectives: To estimate the incidence of clinical fragility fractures in postmenopausal women with rheumatoid arthritis (RA) and analyze risk factors for fracture.
Methods: Incidence of clinical fragility fractures in 330 postmenopausal women with RA was compared to that of a control population of 660 age-matched postmenopausal Spanish women. Clinical fractures during the previous five years were recorded. We analyzed associations with risk factors for fracture in both populations and with disease-related variables in RA patients.

* Corresponding author at: Rheumatology Department, Hospital Universitari de Bellvitge, Feixa Llarga s/n, 08907 L'Hospitalet, Barcelona, Spain.
E-mail address: carmen.gomez@bellvitgehospital.cat (C. Gómez-Vaquero).

https://doi.org/10.1016/j.bone.2022.116654
Received 26 June 2022; Received in revised form 20 December 2022; Accepted 21 December 2022
Available online 28 December 2022

Results: Median age of RA patients was 64 years; median RA duration was eight years. Sixty-nine percent were in remission or on low activity. Eighty-five percent had received glucocorticoids (GCs); 85 %, methotrexate; and 40 %, ≥1 biologic DMARD. Fifty-four patients and 47 controls had ≥1 major osteoporotic fracture (MOF). Incidence of MOFs was 3.55 per 100 patient-year in patients and 0.72 in controls (HR: 2.6). Risk factors for MOFs in RA patients were age, previous fracture, parental hip fracture, years since menopause, BMD, erosions, disease activity and disability, and cumulative dose of GCs. Previous fracture in RA patients was a strong risk for MOFs (HR: 10.37).
Conclusion: Of every 100 postmenopausal Spanish women with RA, 3–4 have a MOF per year. This is more than double that of the general population. A previous fracture poses a high risk for a new fracture. Other classic risk factors for fracture, RA disease activity and disability, and the cumulative dose of GCs are associated with fracture development.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease with joint involvement and extra-articular manifestations. In RA, bone loss occurs at three levels: (1) the joint, which leads to bone erosions; (2) periarticular, which induces juxta-articular osteopenia; and (3) systemic, which results in osteoporosis and fractures [1–3]. With active disease, bone loss takes place mainly during the first year of the disease and correlates with inflammatory disease activity. It is estimated between 5.5 and 10 % at two years [4], having an impact on the risk of fracture [3,5]. Fragility fractures result in decreased quality of life and life expectancy in these patients [6,7]. Achieving an early osteoporosis diagnosis and implementing a prompt intervention may prevent subsequent fractures [8].

The mechanisms of bone loss in RA are related to effects caused by proinflammatory cytokines that are released from inflamed joints into circulation. Increased bone resorption appears to be the result of a combined action between an increased recruitment of osteoclast precursors from the bone marrow and the differentiation of osteoclasts occurring in the presence of high serum concentrations of proinflammatory cytokines [9]. Tumor necrosis factor (TNF) and interleukin (IL) 1, 6 and 17 induce the expression of RANKL and, to a lesser extent, M-CSF. TNF also promotes the production of DKK1 and sclerostin—two Wnt pathway inhibitors that are fundamental in osteoblastogenesis and osteoprotegerin production—thereby, determining bone formation inhibition [10]. This culminates in the uncoupling of bone remodeling, characterized by increased resorption and decreased bone formation, and eventual bone loss. In addition, autoantibodies such as anti-citrullinated protein antibodies (ACPA) favor bone loss in RA [11,12]. ACPA have a direct pathogenic role on joint damage via either direct interaction with preosteoclasts or activation of pro-osteoclastogenic cytokine production by immune cells. ACPA levels has been shown to correlate with bone mineral density (BMD) at the lumbar spine and femoral neck in RA patients, regardless of disease activity [13].

Clinical risk factors for generalized bone loss in RA include classical risk factors for osteoporosis; factors related to disease activity; and treatment with glucocorticoids. In the last decades, advances made in disease treatment have not managed to fully counteract this problem, even though patients have experienced a significant improvement in quality of life [14]. The recent results of a 3-year follow-up of a cohort including 388 RA patients treated with conventional or targeted biologic and synthetic disease-modifying anti-rheumatic drugs (DMARDs) showed that only patients receiving targeted biologic DMARDs had preserved BMD at the lumbar spine and femoral neck. In patients who received antiresorptive or bone-forming drugs, BMD did not decline, irrespective of DMARD used [15].

van Staa et al. found that RA patients of the British General Practice Research Database had an increased risk of fractures at the vertebrae, hip, pelvis, humerus and tibia/fibula [5]. The main factors related to the presentation of fractures included chronic inflammatory activity, immobility and falls, vitamin D deficiency and treatment with glucocorticoids [2,16], as well as opioid and selective serotonin reuptake inhibitor use [17]. In a recent meta-analysis, the incidence of fragility fractures was 1.53 per 100 patient-years, with vertebral fractures accounting for 50 % of all fractures. Patients not treated with glucocorticoids also had an increased incidence of vertebral and hip fractures [18]. Another meta-analysis of 13 studies showed a more increased risk of fracture in patients with RA compared with subjects without RA [19]. We have recently shown that prevalence of vertebral fractures was high in a contemporary cohort of RA when compared with the general population, despite recent therapeutic advances in RA management [20]. By contrast, in the CORRONA registry in North America [21], the risk of vertebral fractures in patients treated with TNF inhibitors was lower than in those receiving methotrexate. With respect to the risk of non-vertebral fractures, there were no significant differences between those patients treated with TNF inhibitors [22] and those treated with non-biologic DMARDs, abatacept or tocilizumab [23].

Incidence of fractures in patients with RA has been assessed in studies with many variations in design, source of participants, sample size and different fracture locations. Most studies were performed before the widespread use of biologic therapies. We, therefore, performed a multicentric case-control study in a clinical setting that aimed to estimate the incidence of fractures in a population of postmenopausal women diagnosed with RA who were undergoing routine follow-up with rheumatologists under a treat-to-target strategy versus the general population. We also aimed to analyze risk factors for fractures in these patients.

2. Material and methods

The study design is a retrospective case-control study: the exposed cohort comprised postmenopausal women diagnosed with RA and the unexposed cohort was population-based, including postmenopausal women without RA. Both cohorts were reported in a previous study [20].

2.1. Subjects and controls

We included 330 postmenopausal women diagnosed with RA undergoing routine follow-up by rheumatologists from across 19 Spanish rheumatology departments, fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria [24]. Patients were randomly selected from each center's registry of regularly controlled RA patients.

The control group consisted of 660 aged-matched postmenopausal Spanish women, in a 1:2 ratio from the Camargo cohort, included between 2006 and 2008 [25,26]. The cohort was recruited to assess the prevalence and incidence of metabolic bone disease and osteoporotic fractures in men over the age of 50 and postmenopausal women visiting a primary care center in northern Spain (Camargo, Cantabria). Exclusion criteria included a previous trauma which could call into question the fragility nature of the fractures or inability to either attend the recruiting primary care center or undergo the planned tests. At the baseline visit, data regarding risk factors for osteoporosis and fractures were recorded;

a structured questionnaire was provided. Five to ten years after the initial visit, patients had a follow-up and data regarding incident fractures were collected.

2.2. Procedures

Either the routine rheumatologist of each patient or the corresponding center investigator made a face-to-face visit to explain the objectives of the study, provide an information sheet and request their signature for a written informed consent. Sociodemographic variables and variables related to RA and its treatment, risk factors for fracture and pharmacologic prevention with anti-osteoporotic drugs were collected.

Fractures were identified by reviewing clinical records from the hospital and/or primary health center. All fractures between 1 January 2013 and 31 December 2017 (the five-year study period) were confirmed by reviewing either written radiographic study reports or emergency department notes. Date and location of the fractures were recorded.

In the face-to-face visit, patients were asked about the mechanism of action of every fracture. Each incident fracture was classified into traumatic and fragility fracture categories. We defined fragility fractures as those resulting in the absence of external injury, such as from falls from one's own height or walking at normal speed.

2.3. Risk factor assessment

The variables analyzed in this study included subject characteristics, indicators of disease severity and risk factors for fracture. To prevent collection of CRP and DAS28 values when calculated only during disease flares, we obtained a minimum of three evaluations/year throughout the study period. With these data, we calculated the mean of the variables only when collected every year (mean DAS28, n: 161, and mean CRP, n: 154). We also calculated the area under the curve of CRP over time as an estimation of disease activity, even when unavailable every year (cumulative mean CRP, n: 269).

We furthermore collected data on BMD at the lumbar spine, femoral neck and total hip using dual-energy x-ray absorptiometry (DXA) (Lunar® or Hologic®, depending on each center). Two-hundred and sixty-seven RA patients had undergone a bone densitometry; not all scans were performed at the time of study inclusion. In the control group, BMD values were collected using Hologic QDR 4500 (Bedford, MA, USA) at inclusion. BMD was expressed as standardized BMD values in mg/cm^2 and T-score.

2.4. Sample size calculation

We estimated the sample size of the exposed cohort, taking into account the incidence of hip fracture published by Lin et al., 2015 [27]. The sample size of the unexposed cohort was estimated based on data from a cohort of individuals from Catalonia, including those aged >50 years with all types of fracture [28]. We assumed an incidence of fracture of 3.26 % for RA and 1.13 % for the unexposed cohort. To detect statistically significant differences between these two incidence rates, with a significance of 5 % and a power of 80 %, a sample of 345 patients was considered necessary for each cohort and a 10 % loss was assumed.

To increase statistical power, two age-matched controls were assigned to each RA patient.

2.5. Statistical analysis

Baseline characteristics of postmenopausal women diagnosed with RA were described using the median and interquartile range (IQR) for continuous variables and frequencies for categorical variables. These characteristics were compared between the two groups using *t*-test or Wilcoxon test for continuous variables and chi-square test for categorical variables.

The global crude incidence of clinical fragility fractures per 100 person-years was estimated for patients. The crude incidence of major osteoporotic fractures (MOFs) (clinical vertebral, hip, forearm and humerus) was estimated for both exposed and unexposed patients; differences were analyzed.

Associations between disease-related risk factors in RA patients and incident fractures were also assessed. The presence of clinical fracture risk factors was compared between RA patients and controls. In the case of variables with different collection criteria, they were only included in the analysis of the respective group. Cox models were used for assessing these associations; respective hazard ratios were presented in tables.

The analysis was done using statistical program R, version 3.5.1.

3. Results

The study included 330 RA patients and a corresponding number of 660 controls. Median age was 64 years for RA patients without any difference with controls. Both groups differed in several risk factors for fractures, including BMD. A higher risk of fracture was present in RA patients; consequently, there was a higher frequency of treatments for osteoporosis (Table 1). Apart from calcium and vitamin D supplements, 109 RA patients (33 %) had received one antiresorptive or bone-forming agent; 30 had received two; and two patients had received three anti-osteoporotic drugs. The corresponding figures for controls were 175 (27 %), six and two, respectively ($p < 0.001$).

Table 1
Comparison between RA patients and controls.

	RA patients (n: 330)	Controls (n: 660)	p value
Age, years	64 [56; 70]	63 [56; 70]	0.925
Age ≥ 65 years	151 (45,8 %)	302 (45.8 %)	1
Body mass index (BMI), kg/m^2	26.22 [23.51; 29.56]	28.08 [25.38; 31.25]	**<0.001**
BMI ≤ 20 kg/m^2	19 (5.8 %)	6 (0.9 %)	**<0.001**
Previous fragility fractures	95 (28.8 %)	109 (16.5 %)	**<0.001**
Parental hip fracture*	43 (13.4 %)	68 (10.3 %)	–
Glucocorticoids	272 (84.7 %)	15 (2.3 %)	**<0.001**
Current smoking	49 (14.9 %)	60 (9.1 %)	**<0.002**
Alcohol†	8 (2.4 %)	75 (11.4 %)	–
Early menopause	56 (1.07 %)	98 (14.9 %)	0.438
Years since menopause	14 [7; 22]	13 [6; 22]	0.194
Standardized bone mineral density (sBMD), n: 274			
Lumbar spine, mg/cm^2	922 [824; 1038]	970 [882; 1067]	**<0.001**
T-score, SD	−1.9 [−2.73; −0.94]	−1.62 [−2.36; −0.77]	**<0.009**
Femoral neck, mg/cm^2	729 [662; 815]	785 [711; 877]	**<0.001**
T-score, SD	−1.7 [−2.22; −1.05]	−1.27 [−1.84; −0.57]	**<0.001**
Total hip, mg/cm^2	798 [711; 882]	858 [774; 939]	**<0.001**
T-score, SD	−1.28 [−1.98; −0.59]	−0.79 [−1.48; −0.13]	**<0.001**
WHO diagnostic categories (n: 274)			**<0.001**
Normal	31 (11.3 %)	136 (20.6 %)	
Osteopenia	139 (50.7 %)	368 (55.8 %)	
Osteoporosis	104 (38.0 %)	156 (23.6 %)	
Treatment for osteoporosis			
Calcium supplements	197 (60 %)	57 (9 %)	**<0.001**
Vitamin D supplements	242 (73 %)	84 (13 %)	**<0.001**
Hormone replacement therapy	5 (2 %)	6 (1 %)	–
Calcitonin	1 (−%)	7 (1 %)	–
Selective Strogen Receptor Modulators (SERM)	1 (−%)	12 (2 %)	**<0.05**
Bisphosphonates	115 (35 %)	164 (25 %)	**<0.001**
Denosumab	44 (14 %)	2 (−%)	**<0.001**
Teriparatide	9 (3 %)	2 (−%)	**<0.01**

Data are presents as n (percentage) or median [IQR]. *In controls, fragility fracture in a first-degree relative. †The collection criteria were different. Significant values are highlighted in bold.

Table 2 depicts characteristics of RA patients. Median RA duration was 8 years. Patients were mostly seropositive and had erosive disease. Two-thirds of patients were in remission or with low activity. During the study period, 72 % of patients had received glucocorticoids; 76 %, methotrexate; and 40 % ≥1 biologic DMARD (29 % had received one; 6 % two; 4 % three; and 1 % four).

In the study period, we identified 105 fractures (87 fragility and 18 traumatic fractures) in 75 RA patients (Table 3). Twenty-three patients had two fractures, whilst another seven patients had three. Apart from MOFs, the most frequent fractures included pelvic branches, ribs and elbows. The most common traumatic fractures were those of the foot and forefoot.

Incidence of fragility fractures in patients with RA was 4.35 per 100 patient-years.

Fifty-four RA patients and 47 controls had ≥1 MOF. Incidence of MOFs was 3.55 per 100 patient-years in RA patients and 0.72 in controls (HR: 2.6 [95 % CI: 1.72–3.94]). Distribution of MOFs was similar in RA patients and controls. Median time to the first MOF was 30 [16; 45] and 45 [28; 50] months in RA patients and controls, respectively (p: 0.019).

Four RA patients (median time to the fracture: 49 [42; 53] months) and no control experienced a hip fracture. All of them had had a fracture before the study period; this was also the case for distal forearm and humerus fractures. Forty-one percent of patients with a vertebral fracture had had a fracture.

Risk factors for MOFs in RA patients were age, previous fracture, parental hip fracture, postmenopausal period duration and proximal femur BMD (both femoral neck and total hip). In controls, risk factors for MOFs were age, age at menopause and lumbar BMD (Table 4).

Among RA-associated factors, MOFs were associated with erosions, disease activity and disability, and cumulative dose of glucocorticoids at the beginning of the study period. The cumulative mean dose of glucocorticoids at first MOF was 13.9 ± 15.4 g (Table 5).

We tested the interaction between RA and several fracture risk factor in a model to assess MOF risk. In this model, the risk of MOF on RA subjects with a previous fracture was strong (HR: 10.37 [95 % CI: 2.95–36.41]) (Table 6).

There was a non-significant trend towards a lower incidence of MOFs in RA with <10 years of evolution when compared to those with >10 years of evolution. Incidence of MOFs in postmenopausal women with <10 years since RA onset was still higher than that in the general population.

Table 2
Main clinical features of RA patients.

RA duration, years	8 [2.5; 15.6]
Rheumatoid factor (RF) +	256 (78 %)
RF titer, IU	84 [40; 216]
Anti-citrullinated protein antibody (ACPA) +	240 (76 %)
ACPA titer, IU	220 [67; 400]
Erosive disease	178 (55 %)
HAQ-8	0.75 [0.12; 1.4]
DAS28 (n: 161)	2.8 [2.37; 3.42]
Remission	76 (41 %)
Low activity	52 (28 %)
Moderate activity	52 (28 %)
High activity	5 (3 %)
C-reactive protein, mg/L (n: 154)	4.8 [2.54; 8.4]
Cumulative C-reactive protein, mg/L (n: 269)	17 [8.4; 31.46]
Glucocorticoids	
During the 5-year study period	230 (72 %)
Since the beginning of RA	272 (85 %)
Cumulative dose to 1 January2013, mg of prednisone or equivalent	7209 [1870; 18,038]
Synthetic DMARD*	303 (92 %)
Methotrexate	
During the 5-year study period	249 (76 %)
Maximum dose, mg/week	15 [12,5; 20]
Treatment duration, months	60 [30; 60]
Since the beginning of RA	261 (85 %)
Leflunomide	100 (30 %)
Hydroxychloroquine	92 (28 %)
Sulfasalazine	16 (5 %)
Gold salts	3 (1 %)
Biologic DMARD*	133 (40 %)
TNF inhibitors	100 (30 %)
Tocilizumab	34 (10 %)
Abatacept	30 (9 %)
Rituximab	20 (6 %)
Targeted synthetic DMARD*	2 (0,6 %)

Data are presents as n (percentage) or median [IQR]. *DMARD: disease-modifying antirheumatic drugs.

Table 3
Number and type of fractures in RA patients.

Localization	Fragility	Traumatic
Face	0	1
Spine	41	1
Ribs	3	0
Pelvic branches	8	0
Sacrum	2	0
Clavicle	0	2
Scapula	0	1
Humerus	8	2
Distal forearm	14	0
Elbow	3	1
Hand	0	2
Hip	4	0
Patella	0	1
Tibia/Fibula	2	1
Ankle	2	0
Foot	0	6

Table 4
Determinants of MOFs: univariant fracture risk analysis by study group.

	RA patients		Controls	
	HR [95 % CI]	p-value	HR [95 % CI]	p-value
Age, years	1.78 [1.36,2.33]	**<0.001**	1.48 [1.12,1.98]	**0.007**
Age ≥ 65 years	1.59 [1.2,2.1]	**0.0014**	1.33 [1,1.78]	0.051
Body mass index, kg/m^2	1 [0.95,1.06]	0.8809	1.04 [0.98,1.1]	0.188
Previous fragility fractures	9.83 [5.26,18.36]	**<0.001**	1.57 [0.8,3.08]	0.193
Parental hip fracture[a]	2.56 [1.39,4.71]	**0.0026**	0.18 [0.03,1.32]	0.092
Glucocorticoids	1.83 [0.73,4.59]	0.1979	3.11 [0.97,10.01]	0.057
Age at menopause, years	0.89 [0.7,1.13]	0.3318	1.45 [1.03,2.03]	**0.031**
Early menopause	1.09 [0.55,2.17]	0.8037	0.38 [0.12,1.22]	0.104
Years since menopause, years	1.06 [1.03,1.08]	**<0.001**	1.02 [0.99,1.05]	0.132
Standardized bone mineral density (sBMD)				
Lumbar spine, mg/cm^2	1 [1,1]	0.0936	1 [1,1]	**0.017**
T-score, SD	1.23 [0.97,1.57]	0.092	1.35 [1.05,1.73]	**0.017**
Femoral neck, mg/cm^2	1 [0.99,1]	**0.003**	1 [1,1]	0.060
T-score, SD	1.76 [1.21,2.56]	**0.003**	1.36 [0.99,1.86]	0.060
Total hip, mg/cm^2	1 [0.99,1]	**0.0019**	1 [1,1]	0.056
T-score, SD	1.72 [1.22,2.42]	**0.0019**	1.33 [0.99,1.77]	0.056

[a] In controls, fragility fracture in a first-degree relative. SD: standard deviation. Significant values are highlighted in bold.

Table 5
RA determinants of MOFs: univariant fracture risk analysis in RA subjects.

RA characteristics	HR [95 % CI]	p-value
RA duration, years	1.02 [0.99,1.04]	0.198
RF +	1.04 [0.55,1.97]	0.911
RF titer	0.98 [0.72,1.33]	0.911
ACPA +	0.98 [0.52,1.83]	0.952
ACPA titer	1.07 [0.82,1.42]	0.611
Erosive disease	1.84 [1.03,3.27]	**0.039**
Mean HAQ-8	1.94 [1.21,3.12]	**0.006**
Mean DAS28	1.05 [0.68,1.61]	0.833
Remission/low activity	Ref	
Moderate activity	0.43 [0.14,1.3]	0.135
High activity	0.8 [0.33,1.93]	0.623
Mean C-reactive protein (CRP), mg/L	1.05 [1,1.09]	0.057
Cumulative mean CRP	1.01 [1,1.02]	0.013
Glucocorticoids		
Cumulative dose to 1 January 2013[a], mg	1.22 [1.01,1.46]	**0.040**
Synthetic DMARD		
Methotrexate	1.15 [0.6,2.18]	0.674
Leflunomide	0.7 [0.38,1.31]	0.262
Hydroxychloroquine	0.72 [0.38,1.38]	0.326
Sulfasalazine	0.36 [0.05,2.6]	0.312
Gold salts	2.79 [0.39,20.21]	0.309
Biologic DMARD		
TNF inhibitors	0.96 [0.54,1.73]	0.902
Tocilizumab	0.68 [0.24,1.87]	0.453
Abatacept	1.03 [0.41,2.59]	0.946
Rituximab	1.67 [0.67,4.2]	0.274
Targeted synthetic DMARD	0 [0,Inf]	0.996

[a] By an increase of one standard deviation (SD). Significant values are highlighted in bold.

Table 6
Determinants of MOFs: fracture risk analysis by RA and the interaction with the analyzed factor.

	Model: RA + Factor + RAxFactor		
	HR RA	HR Factor	HR RAxFactor
Body mass index, kg/m^2	0.74 [0.03,15.89]	0.99 [0.92,1.07]	1.05 [0.94,1.17]
Previous fragility fractures	0.79 [0.4,1.53]	1.32 [0.53,3.27]	**10.37 [2.95,36.41]**
Parental hip fracture hip†	1.99 [1.25,3.17]	0.38 [0.05,3.1]	8.6 [0.76,96.94]
Glucocorticoids	1.13 [0.36,3.57]	1.71 [0.4,7.23]	1.79 [0.25,12.98]
Age at menopause, year	64.96 [0.314142.7]	1.05 [0.96,1.15]	0.94 [0.84,1.04]
Early menopause	2.35 [1.48,3.75]	0.59 [0.16,2.2]	2.25 [0.41,12.34]
Years since menopause, years	1.23 [0.45,3.4]	0.98 [0.92,1.05]	1.04 [0.99,1.09]
Standardized bone mineral density (sBMD)			
Lumbar spine, mg/cm^2	0.63 [0.02,21.75]	1 [0.99,1]	1 [1,1.01]
T-score, SD	3.84 [1.37,10.77]	1.49 [1.07,2.07]	0.85 [0.53,1.35]
Femoral neck, mg/cm^2	11.84 [0.27,518.92]	1 [1,1]	1 [0.99,1]
T-score, SD	1.67 [0.5,5.6]	1.21 [0.81,1.79]	1.31 [0.67,2.53]
Total hip, mg/cm^2	17.78 [0.27,1178.62]	1 [0.99,1]	1 [0.99,1]
T-score, SD	1.52 [0.53,4.36]	1.28 [0.86,1.91]	1.37 [0.72,2.62]

SD: standard deviation. Significant values are highlighted in bold.

4. Discussion

The results of this study demonstrate that contemporary postmenopausal women with RA are at an increased risk of osteoporotic fractures when compared to the general population. The patients included in the study had access to biological treatments and received care with tight-control and treat-to-target strategies; most achieved clinical remission or low disease activity but fracture risk was still elevated.

Incidence of MOFs is 3.55 per 100 patient-years, that is, between 3 and 4 of every 100 postmenopausal women with RA have a MOF per year. This is 2.6 times more than the general population. >60 % of fractures occur at the spine. In our population, disease activity and disability, the cumulative dose of glucocorticoids and mainly previous fractures are associated with the development of new MOFs. Interestingly, incidence of hip fractures found in our study—0.24 per 100 patient-years—matches the previously reported incidence of hip fracture in women with RA from the Spanish National Inpatient Registry, which is estimated at 0.23 per 100 patients-year [29].

A recent systematic review and meta-analysis of the pooled incidence rate of total and fragility fractures in RA [18], including over 280,000 patients across 23 cohort studies, showed that fragility fractures (1.53 per 100 patient-years) accounted for approximately half of all fractures in RA patients (3.30 per 100 patient-years). Incidence of MOFs found in our study exceeds that of this meta-analysis. Incidence of fracture of the individual studies included in the meta-analysis ranges from 0.6 to 3.2, and that reported by our team falls within the upper part of the interval. The reasons for the difference may be that we included only postmenopausal women and that the pooled site-specific incidence rates of vertebral, hip, forearm, and proximal humeral fractures of the meta-analysis (0.75, 0.43, 0.34, and 0.19 per 100 patient-years, respectively) differed from that obtained in our study (2.10, 0.24, 0.87, and 0.49 per 100 patient-years, respectively). In the meta-analysis, clinical vertebral fractures seem to have been underestimated. Differences in identifying fractures between studies are known to be associated with the various methods used to capture such information, i.e., mainly self-reporting; confirmation by x-ray or medical reports in clinical studies; or registry-based study coding. In the case of vertebral fractures, its definition also influences the capture, i.e., clinical or radiologic; x-ray or Vertebral Fracture Assessment; and different semi-quantitative scores. Moreover, in RA patients, characteristics of the population regarding age, sex, disease duration and severity and medication use, as well as its source (rheumatology departments or database studies) highly determine the resultant incidence of fractures. In our study, we searched actively for fractures in RA and controls, confirming all.

Regarding the hazard ratio (HR) of MOFs between RA patients and controls, our study finding of a HR of 2.6 [1.72,3.94] was higher than that in the aforementioned meta-analysis [18] (RR of fragility fractures 1.61, 95 % CI 1.44–1.79) and closer to that of another meta-analysis of 13 studies [19], in which RR was 2.25, 95 % CI [1.76–2.87]. Again, differences in the study designs may explain the results found.

A history of previous fractures is the most important risk factor for the presentation of a new fragility fracture [30,31]. In our study, both general and RA specific factors correlate with the occurrence of MOFs; however, the most striking data is that RA patients with a previous fracture have a 10-fold risk of having a new fragility fracture than RA patients who have not had a fracture before. This highlights the need for strict secondary prevention of fragility fracture in patients with RA and previous fragility fractures.

An increase in the risk of hip, forearm—and particularly—vertebral fractures occurs rapidly after the start of glucocorticoid therapy [32]. It has been reported to occur with doses as small as 2.5–7.5 mg of daily prednisolone [33]. Current low-dose glucocorticoid oral use (≤7.5 mg of prednisolone or equivalent dose/day) in patients with RA has been associated with an elevated risk of clinical vertebral fracture, whilst the risk of fragility fractures at other locations did not rise. The authors hypothesized that the beneficial effect of low-dose glucocorticoid therapy on suppressing inflammation could be enough to offset its negative effect on bone synthesis in most fracture sites, albeit not in vertebrae [34]. A higher cumulative dose of glucocorticoids before the study period rose the risk of presenting a MOF in our RA patients and, more

specifically, that of a vertebral fracture (HR: 1.28 [1.06; 1.54]).

We assessed if fracture incidence in our RA cohort changed over the years, given tight-control and treat-to-target strategies, and the widespread use of biologic DMARDs in the last decade. Therefore, we analyzed the incidence of MOFs in patients with an RA duration of more or <10 years of evolution. There were no differences between these two groups. Accordingly, and as previously mentioned, we found that the risk of morphometric vertebral fractures in this RA cohort was still high when compared with the general population, even in light of recent therapeutic advances [20]. It seems that strategies that have shown the ability to control disease activity are not effective enough to prevent fractures or, conversely, do not fully reach all patients. Similarly, in a recent study from Sweden, patients who were diagnosed with RA in both the 1990s and 2000s had an increased risk of fragility fractures compared with matched controls from the general population. This is despite an improved treatment strategy in the 2000s, when most patients received potent DMARD treatment—primarily methotrexate—during the early disease stage [35].

The strengths of our study include a comparator design involving age-matched women from the same country at a ratio of 1:2 and the multicentric nature of our cohort from specialized rheumatology centers. Limitations of this study include the retrospective collection of the data. Regarding RA variables, we are confident about their accuracy, as they are carefully recorded in medical records of all rheumatologists. We cannot say the same about DAS28 and HAQ-8 scores, given that not all rheumatologists calculate them at every visit and some tend to calculate them only during disease flares. For this reason, we remained extremely strict about assessing the median in the previous five years. Regarding the identification of fractures, we have full, reliable access online to computerized medical records from both emergency and radiology departments and primary care centers. Another limitation of the study is the non-negligible percentage of patients who had received anti-osteoporosis drugs at some point in their evolution. These data, however, do not undervalue the higher incidence of fragility fractures found in our series of RA patients when compared to the control population. Otherwise, the exclusion of these patients would have biased the RA fracture incidence to a falsely low fracture risk population. Finally, it is remarkable that the control group was recruited 10 years before the patients. We have some data about hip fracture trends in Spain [36–38]. We think that these trends scarcely affect the results of our study as the incidence of hip fracture in patients and controls is low. Regarding major fractures, we do not have data on trends in its incidence.

Finding the balance between the incidence of MOFs in our study with that of COVID-19 as a hypothetical comparator, the cumulative new cases of MOFs in RA patients over the past 28 days per 100,000 population would be 272. This corresponds to World Health Organization risk level 3 classification, which is high. In the absence of a vaccine against fractures, we recommend to all rheumatologists that they remain highly vigilant about the risk of fracture in their RA patients, particularly if they have experienced a previous fracture. Rheumatologists should treat these patients as being at high risk. Maintaining disease activity at the lowest level and glucocorticoids at a minimal dose comprise some of the best measures to prevent fragility fractures in RA patients.

5. Conclusion

Contemporary postmenopausal women with RA are at an increased risk of osteoporotic fractures when compared to the general population.

Elevated fracture risk persists despite the high level of disease control achieved with biological treatments and tight-control, treat-to-target strategies.

Incidence of MOFs is 3.55 per 100 patient-years, that is, between 3 and 4 of every 100 postmenopausal women with RA have a MOF per year. This is 2.6 times more than the general population.

More than 60 % of fractures occur at the spine.

In our population, disease activity and disability, the cumulative dose of glucocorticoids and mainly previous fractures are associated with the development of new MOFs.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Camargo cohort was funded in part by a grant from the Instituto de Salud Carlos III (PI21/00532), Ministerio de Economia y Competitividad, Spain, that included FEDER funds from the EU.

Ethics

The study complies with the Declaration of Helsinki. All RA patients provided written informed consent to participate, and the research protocol was approved by the Clinical Research Ethics Committee of the Bellvitge University Hospital as the reference center and in all participating centers, in accordance with the current Spanish legislation and Law 14/2007, of July 3, on Biomedical Research.

The Camargo cohort study was approved by the local Ethics Committee, and all subjects gave written informed consent at the moment of inclusion in the cohort.

Processing, communication and transfer of personal data of all participating subjects has been adjusted to the provisions of Organic Law 15/1999, of December 13, on the protection of personal data. All data were sent fully de-identified.

CRediT authorship contribution statement

Carmen Gómez-Vaquero: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **José Luis Hernández:** Methodology, Investigation, Writing – review & editing. **José Manuel Olmos:** Methodology, Investigation, Writing – review & editing. **Dacia Cerdà:** Investigation, Writing – review & editing. **Cristina Hidalgo Calleja:** Investigation, Writing – review & editing. **Juan Antonio Martínez López:** Investigation, Writing – review & editing. **Luis Arboleya:** Investigation, Writing – review & editing. **Francisco Javier Aguilar del Rey:** Investigation, Writing – review & editing. **Silvia Martinez Pardo:** Investigation, Writing – review & editing. **Inmaculada Ros Vilamajó:** Investigation, Writing – review & editing. **Xavier Surís Armangué:** Investigation, Writing – review & editing. **Dolors Grados:** Investigation, Writing – review & editing. **Chesús Beltrán Audera:** Investigation, Writing – review & editing. **Evelyn Suero-Rosario:** Investigation, Writing – review & editing. **Inmaculada Gómez Gracia:** Investigation, Writing – review & editing. **Asunción Salmoral Chamizo:** Investigation, Writing – review & editing. **Irene Martín-Esteve:** Investigation, Writing – review & editing. **Helena Florez:** Investigation, Writing – review & editing. **Antonio Naranjo:** Investigation, Writing – review & editing. **Santos Castañeda:** Investigation, Writing – review & editing. **Soledad Ojeda Bruno:** Investigation, Writing – review & editing. **Sara García Carazo:** Investigation, Writing – review & editing. **Alberto Garcia-Vadillo:** Investigation, Writing – review & editing. **Laura López Vives:** Investigation, Writing – review & editing. **Àngels Martínez-Ferrer:** Investigation, Writing – review & editing. **Helena Borrell Paños:** Investigation, Writing – review & editing. **Pilar Aguado Acín:** Investigation, Writing – review & editing. **Raul Castellanos-Moreira:** Investigation, Writing – review & editing. **Pau Satorra:** Formal analysis, Writing – review & editing. **Cristian Tebé:** Formal analysis, Writing – review & editing. **Núria Guañabens:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Dr. Gomez-Vaquero has received fees for lectures and/or advice from

Amgen, BMS, Eli Lilly, Gedeon-Richter, Grünenthal, MSD, Novartis, Roche, Stada and UCB.

Dr. Hernandez received grant funding and fees for lectures from Amgen and MSD.

Dr. Olmos has received past fees for lectures from Amgen, Eli Lilly, Stada and Gedeon-Richter.

Dr. Naranjo has received past fees for lectures and/or advice from Amgen and UCB.

Dr. Castañeda has received fees for lectures and/or advice from Amgen, BMS, Eli- Lilly, Gedeon-Richter, Grünenthal, MSD, Novartis, Pfizer, Roche, Sanofi, Stada and UCB.

Dr. Garcia-Vadillo has received past fees for lectures from Amgen, Eli Lilly, UCB, Stada and Gedeon-Richter.

Dr. Aguado Acin has received fees for lectures and/or advice from Abbie, Alexion, Amgen, Astra Zeneca, Eli Lilly, Faes, Gedeon-Richter, GP Pharm, Kyowa Kirin, MSD, Rubió and Theramex.

Dr. Castellanos-Moreira has received past fees for lectures and/or advice from Pfizer, Lilly, UCB and BMS.

Dr. Tebe has received fees for lectures from Amgen, Boehringer Ingelheim, and Gedeon Richter.

Dr. Guañabens has received past fees for lectures and/or advice from Alexion, Amgen, Eli Lilly and UCB.

The remaining authors have no competing interests to disclose.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Acknowledgements

The authors gratefully acknowledge members from the Spanish Society of the Rheumatology Research Unit for their assistance in designing the study.

References

[1] H.G. Raterman, I.E. Bultink, W.F. Lems, Osteoporosis in patients with rheumatoid arthritis: an update in epidemiology, pathogenesis, and fracture prevention, Expert. Opin. Pharmacother. 21 (2020) 1725–1737.
[2] L. Heinlen, M.B. Humphrey, Skeletal complications of rheumatoid arthritis, Osteoporos. Int. 28 (2017) 2801–2812.
[3] B. Chen, G. Cheng, H. Wang, Y. Feng, Increased risk of vertebral fracture in patients with rheumatoid arthritis: a meta-analysis, Medicine (Baltimore) 95 (2016), e5262.
[4] A.K. Gough, J. Lilley, S. Eyre, R.L. Holder, P. Emery, Generalised bone loss in patients with early rheumatoid arthritis, Lancet 344 (1994) 23–27.
[5] T.P. van Staa, P. Geusens, J.W. Bijlsma, H.G. Leufkens, C. Cooper, Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis, Arthritis Rheum. 54 (2006) 3104–3112.
[6] D. Bliuc, N.D. Nguyen, V.E. Milch, T.V. Nguyen, J.A. Eisman, J.R. Center, Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women, JAMA 301 (2009) 513–521.
[7] I.E.M. Bultink, M. Vis, I.E. Van Der Horst-Bruinsma, W.F. Lems, Inflammatory rheumatic disorders and bone, Curr. Rheumatol. Rep. 14 (2012) 224–230.
[8] J.R. Tucci, Importance of early diagnosis and treatment of osteoporosis to prevent fractures, Am. J. Manag. Care 12 (2006) S181–S190.
[9] G. Schett, Osteoimmunology in rheumatic diseases, Arthritis Res Ther 11 (2009) 210.
[10] G. Schett, K.G. Saag, J.W. Bijlsma, From bone biology to clinical outcome: state of the art and future perspectives, Ann. Rheum. Dis. 69 (2010) 1415–1419.
[11] U. Harre, D. Georgess, H. Bang, A. Bozec, R. Axmann, E. Ossipova, et al., Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin, J. Clin. Invest. 122 (2012) 1791–1802.
[12] S. Bugatti, L. Bogliolo, B. Vitolo, A. Manzo, C. Montecucco, R. Caporali, Anti-citrullinated protein antibodies and high levels of rheumatoid factor are associated with systemic bone loss in patients with early untreated rheumatoid arthritis, Arthritis Res. Ther. 18 (2016) 226.
[13] I. Llorente, L. Merino, A.M. Ortiz, E. Escolano, S. González-Ortega, R. García-Vicuña, et al., Anti-citrullinated protein antibodies are associated with decreased bone mineral density: baseline data from a register of early arthritis patients, Rheumatol. Int. 37 (2017) 799–806.
[14] B. Hauser, P.L. Riches, J.F. Wilson, A.E. Horne, S.H. Ralston, Prevalence and clinical prediction of osteoporosis in a contemporary cohort of patients with rheumatoid arthritis, Rheumatology (Oxford) 53 (2014) 1759–1766.
[15] J.F. Chen, C.Y. Hsu, S.F. Yu, C.H. Ko, W.C. Chiu, H.M. Lai, et al., The impact of long-term biologics/target therapy on bone mineral density in rheumatoid arthritis: a propensity score-matched analysis, Rheumatology (Oxford) 59 (2020) 2471–2480.
[16] K. Briot, P. Geusens, I. Em Bultink, W.F. Lems, C. Roux, Inflammatory diseases and bone fragility, Osteoporos. Int. 28 (2017) 3301–3314.
[17] G. Ozen, S. Pedro, F. Wolfe, K. Michaud, Medications associated with fracture risk in patients with rheumatoid arthritis, Ann. Rheum. Dis. 78 (2019) 1041–1047.
[18] S. Jin, E. Hsieh, L. Peng, C. Yu, Y. Wang, C. Wu, et al., Incidence of fractures among patients with rheumatoid arthritis: a systematic review and meta-analysis, Osteoporos. Int. 29 (2018) 1263–1275.
[19] A.L. Xue, S.Y. Wu, L. Jiang, A.M. Feng, H.F. Guo, P. Zhao, Bone fracture risk in patients with rheumatoid arthritis: a meta-analysis, Medicine (Baltimore) 96 (2017), e6983.
[20] N. Guañabens, J.M. Olmos, J.L. Hernández, D. Cerdà, C. Hidalgo Calleja, J. A. Martínez López, et al., OsteoResSer Working Group of the Spanish Society of Rheumatology. Vertebral fractures are increased in rheumatoid arthritis despite recent therapeutic advances: a case-control study, Osteoporos. Int. 32 (2021) 1333–1342.
[21] K.A. Coulson, G. Reed, B.E. Gilliam, J.M. Kremer, P.H. Pepmueller, Factors influencing fracture risk, T score, and management of osteoporosis in patients with rheumatoid arthritis in the consortium of rheumatology researchers of North America (CORRONA) registry, J. Clin. Rheumatol. 15 (2009) 155–160.
[22] S.Y. Kim, S. Schneeweiss, J. Liu, D.H. Solomon, Effects of disease-modifying antirheumatic drugs on nonvertebral fracture risk in rheumatoid arthritis: a population-based cohort study, Journal Bone Miner Res 27 (2012) 789–796.
[23] A. Shin, E.H. Park, Y.-H. Dong, Y.-J. Ha, Y.J. Lee, E.B. Lee, et al., Comparative risk of osteoporotic fracture among patients with rheumatoid arthritis receiving TNF inhibitors versus other biologics: a cohort study, Osteoporos. Int. 31 (2020) 2131–2139.
[24] D. Aletaha, T. Neogi, A.J. Silman, J. Funovits, D.T. Felson, C.O. Bingham 3rd, et al., 2010 rheumatoid arthritis classification criteria: an american College of Rheumatology/European league against rheumatism collaborative initiative, Ann. Rheum. Dis. 69 (2010) 1580–1588.
[25] J. Martínez, J.M. Olmos, J.L. Hernández, G. Pinedo, J. Llorca, E. Obregón, et al., Bone turnover markers in spanish postmenopausal women: the Camargo cohort study, Clin. Chim. Acta 409 (2009) 70–74.
[26] J.M. Olmos, J.L. Hernández, P. García-Velasco, J. Martínez, J. Llorca, J. González-Macías, Serum 25-hydroxyvitamin D, parathyroid hormone, calcium intake, and bone mineral density in Spanish adults, Osteoporos. Int. 27 (2016) 105–113.
[27] Y.C. Lin, Y.H. Li, C.H. Chang, C.C. Hu, D.W. Chen, P.H. Hsieh, et al., Rheumatoid arthritis patients with hip fracture: a nationwide study, Osteoporos. Int. 26 (2015) 811–817.
[28] A. Pagès-Castellà, C. Carbonell-Abella, F.F. Avilés, M. Alzamora, J.M. Baena-Díez, D.M. Laguna, et al., Burden of osteoporotic fractures in primary health care in Catalonia (Spain): a population-based study, BMC Musculoskelet. Disord. 13 (2012) 79.
[29] R. Mazzucchelli, E. Pérez Fernandez, N. Crespí-Villarías, J. Quirós-Donate, A. García Vadillo, M. Espinosa, et al., Trends in hip fracture in patients with rheumatoid arthritis: results from the Spanish National Inpatient Registry over a 17-year period (1999-2015). TREND-AR study, RMD Open 4 (2018), e000671.
[30] M.A. Clynes, K. Jameson, D. Prieto-Alhambra, N.C. Harvey, C. Cooper, E. M. Dennison, Impact of rheumatoid arthritis and its management on falls, fracture and bone mineral density in UK biobank, Front. Endocrinol. (Lausanne) 10 (2019) 817.
[31] P.H. Lin, S.F. Yu, J.F. Chen, Y.C. Chen, H.M. Lai, W.C. Chiu, et al., Risk factor analysis of fragility fractures in rheumatoid arthritis: a 3-year longitudinal, real-world, observational, cohort study, PLoS One 16 (2021), e0255542.
[32] M. Güler-Yüksel, J.N. Hoes, I.E.M. Bultink, W.F. Lems, Glucocorticoids, inflammation and bone, Calcif. Tissue Int. 102 (2018) 592–606.
[33] T.P. Van Staa, H.G. Leufkens, L. Abenhaim, et al., Use of oral corticosteroids and risk of fractures, J. Bone Miner. Res. 15 (2000) 993–1000.
[34] S. Abtahi, Driessen JHM, A.M. Burden, P.C. Souverein, J.P. van den Bergh, T.P. van Staa, et al., Low-dose oral glucocorticoid therapy and risk of osteoporotic fractures in patients with rheumatoid arthritis: a cohort study using the Clinical Practice Research Datalink, Rheumatology (Oxford) 61 (2022) 1448–1458.
[35] B.M. Nyhäll-Wåhlin, S. Ajeganova, I.F. Petersson, M. Andersson, Increased risk of osteoporotic fractures in swedish patients with rheumatoid arthritis despite early treatment with potent disease-modifying anti-rheumatic drugs: a prospective general population-matched cohort study, Scand. J. Rheumatol. 48 (2019) 431–438.
[36] J.L. Hernández, J.M. Olmos, M.A. Alonso, C.R. González-Fernández, J. Martínez, M. Pajarón, et al., Trend in hip fracture epidemiology over a 14-year period in a spanish population, Osteoporos. Int. 17 (2006) 464–470.
[37] R. Mazzucchelli Esteban, E. Pérez-Fernández, N. Crespí-Villarías, A. García-Vadillo, G. Rodriguez-Caravaca, A. Gil de Miguel, et al., Trends in osteoporotic hip fracture epidemiology over a 17-year period in a spanish population: Alcorcón 1999–2015, Arch. Osteoporos. 12 (2017) 6.
[38] R. Azagra, F. López-Expósito, J.C. Martin-Sánchez, A. Aguyé, N. Moreno, C. Cooper, et al., Changing trends in the epidemiology of hip fracture in Spain, Osteoporos. Int. 25 (2014) 1267–1274.