Advances in Rheumatology

RESEARCH Open Access

Osteoporotic fractures in rheumatoid arthritis patients in Argentina: a matched retrospective cohort study

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Abstract

Background: To compare the incidence of osteoporotic fractures in patients with rheumatoid arthritis (RA) with matched controls from a university hospital.

Methods: Consecutive RA patients ($n = 100$) were matched (age and sex) with controls (1:2). The follow-up period began at the index date, defined as the date of diagnosis for RA patients and the date of the first medical claim at the Health Management Organization (HMO) for non-RA patients. Fracture incidence rates per 1000 persons-years (PY) for distinct types of fractures were calculated. Multivariate cox regression analysis was performed to identify factors associated with fractures.

Results: One hundred RA patients were followed for a total of 975.1 patients-years and 200 controls for 1485.7 patients-years. No difference was found in the overall fracture incidence rate per 1000 PY between RA and controls (19.5, 95% CI 12.7–28.6 vs 12.1, 95% CI 7.7–18.7, $p = 0.07$). In the Cox regression analysis, only age (HR 1.06, 95% CI 1.02–1.11, $p = 0.006$) and history of a prior fracture (HR 9.85, 95% CI 2.97–32.64, $p < 0.001$) were associated with fractures after the index date. The stratified analysis of the fractures by location showed that only the vertebral fractures were more frequent in RA patients compared with controls (12.9 per 1000 PY, 95% CI 8.9–25.8, vs. 3.4, 95% CI 1.4–8.1, respectively, $p = 0.01$).

Conclusion: Patients with RA didn't show an overall increased risk of osteoporotic fractures compared with matched controls, but vertebral fractures were more frequently observed in patients with RA.

Keywords: Rheumatoid arthritis, Incidence, Osteoporosis, Fragility fractures, Glucocorticoids

Introduction

Osteoporosis (OP) is a systemic skeletal disease characterized by decreased bone strength with a consequent increase in bone fragility and susceptibility to fracture due to low bone mass and microarchitecture alterations that generate a reduction of bone resistance to torsion and compression [1–3]. These fractures, known as fragility fractures, are bone cracks caused by a low-energy trauma (i.e. falling from a standing height) that should not be able to break a healthy bone [4].

OP is a very prevalent condition that affects over 200 million people worldwide and causes an important economic and health burden. The principal risk factors for OP are sex and age, and it is estimated to affect 50% of women and 20% of men over 50 years [5]. The incidence of hip fractures in Argentina for women over 50 years is 276.5 per 100,000 person-years, and 114.7 every 100,000 person-years for men [4, 6–8]. The LAVOS study (Latin American Study of Vertebral Osteoporosis) showed an estimated vertebral fractures' prevalence of 16.2% [9]. Fragility fractures can be underdiagnosed because they are frequently non-symptomatic and consequently, not registered [6–8, 10, 11].

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On the other hand, Rheumatoid Arthritis is the most frequent inflammatory arthritis in the adult population, affecting between 0.3 and 1% of the population in Argentina [12, 13]. It is an important risk factor for osteoporosis and osteoporotic fractures [4] since it affects bone structure in a multifactorial fashion, including chronic inflammation [14], immobility, use of corticosteroids (GC), vitamin D deficiency, and augmented fall risk [15]. Nevertheless, the relative weight of each of these factors is still unknown [16, 17]. Current data suggests that the pro-inflammatory cytokines (TNF-α, IL-1, IL-6, and IL-17) enhance the expression of RANKL (Receptor Activator of NF-kβ Ligand), leading to increased osteoclast differentiation, and thereafter producing bone resorption [14, 15, 18].

Several recently published studies show the impact of corticosteroids on bone mineral density (BMD) in patients with RA. Cheng T. et al. found that those patients with RA who received low doses of GC had a lower BMD at the spine (L1–4), a higher rate of fractures, and a significantly higher risk of fractures after 10 years compared to patients with RA who did not receive treatment with GC [19]. There is scarce literature in Latin America regarding the incidence of osteoporotic fractures in patients with RA. Moreover, the numerous advances in recent years for the treatment of RA may have changed the OP epidemiology in these patients. Our objective was to compare the incidence of fragility fractures in rheumatoid arthritis patients diagnosed after the year 2000 with matched controls from a University hospital-based health management organization (HMO) [13, 20–23].

Materials and methods

Data source and study population

We performed a retrospective cohort study on patients enrolled in a HMO in Buenos Aires City, Argentina. We included 100 consecutive incident RA patients diagnosed at our rheumatology unit between 01/01/2000 and 31/12/2015, that fulfilled ACR/EULAR 2010 criteria [24], and 200 controls (1:2) matched by age at diagnosis of RA and by sex.

We excluded all patients who suffered fragility fractures prior to the diagnosis of RA, or regarding controls, before the date of diagnosis of RA of their matched patient (Index Date). Patients who were affiliated to the HMO for under a year were also excluded to avoid possible prevalent cases that might have been affiliated to the HMO with the disease (RA or fractures).

The follow-up period began at the index date, defined as the date of RA diagnosis for cases and the date of the first medical claim at the HMO for the non-RA patients. Subjects were followed until they voluntarily left the HMO, death, or the end of study (05/01/2018).

We reviewed each patient's electronic medical records and recorded demographic information (sex and age), clinical data (comorbidities, weight, body mass index, current or past smoking, type and location of fracture), laboratory results (positivity for anti-citrullinated peptide antibody and/or rheumatoid factor, erythrosedimentation rate, ultrasensitive c reactive protein at the time of diagnosis), images (annual bone densitometry) and treatment data (chronic use of corticosteroid, use of another immunosuppressant, treatment for osteoporosis and osteopenia). We defined low-dose of GC as a 2.5–7.5 mg/day of prednisone or equivalent dose and prolonged corticosteroid use as equal or more than 3 months of use.

Fractures were evaluated by using X-rays, Computerized Tomography, and Nuclear Magnetic Resonance, many of which were ordered by other specialists for many other clinical reasons. All images that allowed to see the bones were carefully reviewed looking for fractures. Vertebral morphology of fractures was evaluated by Genant Classification [25].

The primary outcome was the incidence rate of all new fragility fractures after the index date, defined as bone cracks caused by a low-energy trauma [26]; and the secondary outcomes were incidence rates of each site fragility fractures (ribs, proximal extremity of the femur/hip, pelvis, vertebra, humerus, distal extremity of the radius and ulna). We excluded fractures produced by high impact trauma and fractures in sites that are not mentioned above.

Statistical analysis

Descriptive statistics were performed. Categorical variables were expressed as percentages with their corresponding 95% confidence intervals (95% CI). Continuous variables were expressed as means and medians, according to their distribution, with their corresponding standard deviations (SD) or interquartile ranges (IQR). Categorical variables were compared using a chi-square test or Fisher's test, and continuous variables using Student's t-test or Mann's Whitney test.

The incidence rates for all fractures and for each type of fragility fracture (vertebral, radius and femur) were calculated, both for patients with rheumatoid arthritis and controls, and the rate ratio between both groups was reported. The analysis was done at fracture level and not at patient level (each patient could have had more than one fracture after the index date).

We then performed a multivariate logistic regression analysis, evaluating possible factors associated with fractures (RA diagnosis, treatment with biologic DMARDs, sex, age, prior fracture after the index date, prolonged corticosteroid use – equal or more than 3 months-, osteoporosis diagnosis, osteoporosis treatment).

Results

Patient's demographic and clinical characteristics

One hundred patients with RA and 200 age and sex-matched controls were included. RA patients were followed for a total of 975.1 patients-years (PY) and controls for 1485.7 patients-years. As shown in Tables 1, 78% were female in both groups and the mean age at index date was 62 years. The median duration of follow-up was 9.5 years (IQR 5.9–13.4) for the RA group and 7.4 years (IQR 2.4–12.3) for the control group.

Regarding the RA patients, 97.9% (95% CI 92.0–99.5) were seropositive for Rheumatoid Factor and/or Anti Citrullinated Peptide Antibodies (ACPA), 94% (95% CI 87.1–97.3) were treated with conventional Disease-Modifying Antirheumatic Drugs (DMARDs), and 20% (95% CI 13.2–29.1) with biologic DMARDs. Sixty-nine percent of the patients with RA (69.0%, CI 0.59–77.3) used GC at some time of their disease vs. 5 patients in the control group (2.5%, CI 1.0–5.9), being this difference statistically significant ($p < 0.001$). In the same line, there was a statistically significant difference between groups ($p < 0.001$) for the prolonged use of GC, showing that 63 RA patients were exposed to prolonged GC (63.0%, CI 53.1–71.9) ($p < 0.001$) vs. 4 controls (2.0%, CI 0.7–5.2).

At least one Bone Mineral Density test was performed during follow-up in 74 of the RA patients (74, 95% CI 64.4–81.7) and in 88 of controls (44, 95% CI 37.2–50.9), $p < 0.001$. Osteoporosis was diagnosed by BMD in 36.5% (95% CI 26.2–48.1) of RA patients and 27.3% (CI 18.9–37.6) of controls, $p = 0.21$, according to The International Society for Clinical Densitometry (ISCD) [27] and WHO criteria [28]. There was no statistically significant difference in the use of antiresortive treatment between patients with RA (24, 95% CI 16.6–33.4) and controls (15, 95% CI 10.7–20.7) ($p = 0.06$).

Fractures incidence rates

The 100 RA patients contributed with a total of 975.1 patients/years, and showed a global fracture incidence rate of 19.5/1000 PY (95% CI 12.7–28.6) with 25 fractures occurring in 16 patients. The control group contributed with a total of 1485.7 patients/years, and presented a fracture incidence rate of 12.1/1000 PY (95% CI 7.7–18.7), with 23 fractures in 15 patients. The between-group difference is non-significant ($p = 0.07$).

When analyzing each type of fracture, only the vertebral fractures were more frequently found in RA patients compared with controls (12.9 per 1000 PY, 95% CI 8.9–25.8, versus 3.4, 95% CI 1.4–8.1, $p = 0.01$, respectively) (Table 2). The remaining incidence rates for other site fractures were similar across groups (Table 2).

Cox regression analysis association between fracture and other factors

After adjusting for RA diagnosis, treatment with biologic DMARDs, sex, age, history of prior fracture after the index date, prolonged corticosteroid use, osteoporosis diagnosis and treatment for osteoporosis, we found that age (HR 1.06, 95% CI 1.02–1.11, $p = 0.006$) and a

Table 1 Patient characteristics

	RA patients ($n = 100$)	Controls ($n = 200$)	p
Age at index date, years, mean (SD)	62.1 (12.9)	62.4 (13.9)	0.87
Female, n (%, 95 CI)	78 (78, 68.7–85.1)	156 (78, 71.7–83.2)	1
Follow up, years, median (IQR)	9.5 (5.9–13.4)	7.4 (IQR 2.4–12.3)	**< 0.001**
Seropositive Rheumatoid Factor and/or ACPA, n (%, 95 CI)	97,7 (97,7, 92.0–99.5)		
Use DMARDs, n (%, 95 CI)	94 (94, 87.1–97.3)		
Use biologic DMARDs, n (%, 95 CI)	20 (20, 13.2–29.1)		
BMI < 20, n (%, 95 CI)	5 (5.3, 2.2–12.1)	1 (0.6, 0.1–4.3)	**0.02**
Ever Smoker, n (%, 95 CI)	33 (33, 24.4–42.9)	31 (15.6, 11.1–21.3)	**0.001**
Menopause age, years, median (IQR)	47.8 (40.7–51)	48.4 (44.6–51.4)	0.27
Age at first Bone Mineral Densitometry, years, median (IQR)	62.7 (54.4–74.8)	67.0 (58.9–75.5)	0.09
Osteopenia at first densitometry, n (%, 95 CI)	21 (28.4, 19.2–39.8)	31 (35.6, 26.2–46.3)	0.33
Osteoporosis at first densitometry, n (%, 95 CI)	23 (31.3, 21.5–42.6)	22 (25, 16.9–35.2)	0.39
Osteoporosis at any densitometry, n (%, 95 CI)	27 (36.5, 26.2–48.1)	24 (27.3, 18.9–37.6)	0.21
Anti-resorptives use ever, n (% 95 CI)	24 (24.0%, 16.6–33.4)	30 (15.0%, 10.7–20.7)	0.06
Corticosteroid use ever, n (%, 95 CI)	69 (69.0, 59.2–77.3)	5 (2.5, 1.0–5.9)	**< 0.001**
Prednisone use > = 20 mg/day ever, n (%, 95 CI)	5 (5.0, 2.1–11.5)	1 (0.5, 0.1–3.5)	**0.01**
Corticosteroid use > = 3 months, n (%, 95 CI)	63 (63.0, 53.1–71.9)	4 (2.0, 0.7–5.2)	**< 0.001**

Table 2 Incidence rates of distinct types of fractures

	RA patients ($n = 100$)			Controls ($n = 200$)			*P* value
	Number of fractures	Patient/ years	Incidence rate per 1000 persons/years (95% CI)	Number of fractures	Patient/ years	Incidence rate per 1000 persons/years (95% CI)	
All fractures	24	1230.76	19.5 (12.7–28.6)	23	1900.82	12.1 (7.7–18.7)	0.07
Vertebral fractures	9	697.67	12.9 (8.9–25.8)	5	1470.58	3.4 (1.4–8.1)	**0.01**
Radius fracture	5	675.67	7.4 (3.6–14.9)	4	851.06	4.7 (2.3–9.8)	0.21
Ulna fracture	1	1000	1.0 (0.1–7.1)	1	1428.57	0.7 (0.1–4.7)	0.39
Humerus fracture	1	1000	1.0 (0.1–7.1)	5	1219.51	4.1 (1.8–8.9)	0.09
Rib fracture	0	0	0	1	1428.57	0.7 (0.1–4.7)	0.30
Hip fracture	5	793.65	6.3 (2.8–13.4)	5	1470.58	3.4 (1.4–8.0)	0.16
Pelvis fracture	2	625	3.2 (0.9–9.4)	2	1428.57	1.4 (0.3–5.3)	0.19

previous fracture (after index date) (HR 9.85, 95% CI 2.97–32.64, $p < 0.001$) were the only variables independently associated with fragility fractures. Neither RA diagnosis (HR 0.86, 95% CI 0.24–3.07, $p = 0.81$) nor a prolonged use (> 3 months) of low dose corticosteroids (HR 1.57, 95% CI 0.39–6.23, $p = 0.52$) were associated with increased fracture risk.

When analyzing vertebral fractures separately in a multivariate cox regression analysis (adjusting for age, RA diagnosis, gender, and a prior fracture), the use of low dose corticosteroids for more than 3 months was not associated in these patients with an increased vertebral fracture risk (HR 3.43, 95% CI 0.74–15.82, $p = 0.11$).

Discussion

Osteoporosis risk in RA patients is influenced by both general background factors (such as female gender, body mass index, age) and RA specific factors (ACPAs positivity, disease activity, immobility, systemic inflammation, and treatments) [29]. Additionally, the GIOTTO study reported that RA patients received sub-optimal prevention of BMD loss [30].

Since sex, age, and having had a prior fragility fracture are well-known risk factors for fragility fractures [16, 31, 32], we matched RA patients with controls by sex and age, and excluded any patient who had fragility fractures prior to the index date.

Our study shows a similar incidence rate of fragility fractures in RA patients compared with a recent systematic review and meta-analyses 19.5 (95% CI 12.7–28.6) vs 15.31 (95% CI 10.43–22.47) per 1000 persons/years [33].

We did not find an overall increased incidence of fragility fractures in RA patients compared to the general population. We acknowledge that our data differs from most previous studies, which suggested a causal relationship between RA and fragility fractures [17, 19, 32–35]. A possible explanation for the discordance between our results and many of the previous studies in patients with RA is that we included patients diagnosed with RA after the year 2000, when several new and more effective treatment options – Biologic DMARDs – were developed, and when the "treat to target" strategy was incorporated to daily practice, leading to better control of RA activity and consequently, lowering the need for corticosteroids [36]. Although conventional DMARDs diminish the activity of pro-inflammatory cytokines, it is reported that biological DMARDs have a better protective effect on the bone [37] by suppressing inflammation [38], and hence, they might protect the bone from fractures. Only 20% of this cohort of RA patients were in treatment with biologic DMARDs, so we couldn't demonstrate a protective effect regarding fractures, perhaps due to the low number of cases.

In line with this, a recent meta-analysis suggested that there might be a change in fracture risk trends as a result of the change in therapeutic strategies in RA and earlier control of inflammation [33].

Vertebral fractures were the only type of fragility fractures that were more frequent in RA patients than in the general population in our study. On the multivariate logistic regression analysis, the only independently associated variables were age and history of previous fractures. Unfortunately, we could not analyze factors such as BMD in all patients and functional disability which could be associated with fractures. The possibility of finding differences between groups in the rate of osteoporosis might have been hampered by the statistically significant difference of BMD tests performed (77% vs. 44%, $p < 0.001$), explained by the increased awareness of the risk in RA patients and the fact that most of the

controls did not have indication for screening of osteoporosis.

Remarkably, 35% of the patients with RA diagnosed with osteoporosis by BMD test and 45% of controls were not under antiresortive treatment. Although we cannot rule out that it might respond to the retrospective nature of this study and under-registration of the treatment, we believe that it might reflect real life up to some extent and the fact that patients diagnosed with OP often go undertreated until they have a fragility fracture.

Although steroids use is associated with loss of trabecular bone, the main component of vertebrae, we did not find an association between vertebral fractures and prolonged use of low-dose corticosteroids. We don't have a certain explanation for this, but we believe that although more than half of RA patients (63, 95% CI 53.1–71.9, Table 1) were on corticosteroids for more than 3 months, doses were in general low, and only 5% (95% CI 2.1–11.5, Table 1) of patients have ever received prednisone doses greater than 20 mg/d and low doses may not have had an impact on fractures risk.

Our finding on vertebral fractures is in opposition to the study by Kim D. et al. [17], where they found an increased risk on RA patients with longer duration and a higher dose of oral corticosteroids.

Despite radius is also mostly composed of trabecular bone, we did not find a higher incidence rate of fractures in patients with RA compared with controls.

Regarding the incidence of fragility fractures in controls, we found an incidence rate for hip fractures of 3.4 (95% CI 1.4–8.0) per 1000 persons/years. This result is similar to previous studies reported in Argentina, such as the study by A. Wittich et al. in Tucumán [6] with an incidence rate of 2.76 and 1.14 per 1000 persons/years for women and men respectively; the study by M. Morosano et al. in Rosario with 2.9 per 1000 persons/years [7]; and the study by A. Bagur et al. in La Plata with 3.79 and 1.01 per 1000 persons/year for women and men respectively [8]. Regarding the incidence rate of vertebral fractures in controls, our cohort shows an incidence of 3.4 per 1000 persons/years (95% CI 1.4–8.0), but we didn't find any another study in Argentina or Latin America to compare with. Recently, a worldwide study by Ballane, G. et al. [39], reported higher age-standardized incidence rates of vertebral fractures in South Korea (5,44 and 15,75 for men and women per 1000 persons/year), USA (7,07 and 10,83 for men and women per 1000 persons/year) and Hong Kong (2,02 y 7,64 for men and women per 1000 persons/year); and the lowest incidence for the UK (0,48 and 0,84 for women and men per 1000 persons/year). The incidence rate for vertebral fractures reported in our study was similar to Germany (0.87 and 2.05 for men and women per 1000 persons/year) and Italy (2.11 and 2.49 for men and women per 1000 persons/year), within the range of lower values.

This study has several limitations. Due to the retrospective nature of the study, we lacked information on some possible risk factors for osteoporosis, such as functional disability, malabsorption, vitamin D levels, supplementation with vitamin D or calcium, and RA disease activity. We were also unable to stratify patients according to FRAX and to properly register the RA disease activity and its relationship with fracture risk.

On the other hand, some strengths should be listed. First, our HMO offers comprehensive health and medical services to approximately 140,000 outpatients on two central hospitals and 24 peripheral centers, and is broadly representative of the population from Buenos Aires city [13]. Second, all included patients fulfill strict classification criteria, and were compared with 2 matched controls. Third, only patients with incident diagnosis of RA were included and only incident fractures were considered. Finally, we included all types of fragility fractures in the analysis. Since less than half of vertebral fractures are symptomatic, we performed a revision of all the dorsal and lumbar spine x-rays, eliminating the possibility of under-diagnosis of asymptomatic fractures.

Conclusions

In this cohort of RA patients with diagnosis after the year 2000, no overall increased risk of fractures was found in comparison with matched controls, but an increased incidence of vertebral fractures in these patients versus matched controls was found.

Acknowledgements

Not applicable.

Authors' contributions

FP, MB and VS performed the examination of the patients' data in medical records and were a major contribution in writing the manuscript. MS, JR and ERS analyzed and interpreted the patient data statistically. All authors read and approved the final manuscript.

Authors' information

Not applicable.

Funding

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the Good Clinical Practice (GCP) guidelines, defined in the International Conference on Harmonization (ICH), and in accordance with the ethical principles detailed in the European Union Directive 2001/20 (EC) and the federal of the United States Code (Title 21, Part 50 (21CFR50). The study was approved by Institutional Review Board

(IRB00010193, protocol #3518). Since this is a retrospective study, formal consent is not required.

Consent for publication
Not applicable.

Competing interests
- Pierini M.D.; Brom M.D.; Scaglioni M.D.; Scolnik M.D. and Rosa M.D. declare no conflicts of interest.
- Soriano M.D.: has received in the past speaker's honorarium from AbbVie, Novartis, Bristol MS, Novartis, Eli Lilly, Genzyme, Pfizer, Amgen, and Roche. He is on the advisory board for Novartis, AbbVie, Pfizer, Eli Lilly, Sanofi, Sandoz, Amgen. He has received grant from Roche, Novartis, AbbVie, Glaxo Smith Kline.

Received: 21 August 2020 Accepted: 25 March 2021
Published online: 07 April 2021

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