ORIGINAL ARTICLES

FRAX 10-year fracture risk in rheumatoid arthritis assessed with and without bone mineral density – are we treating our patients under bDMARDs?

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ABSTRACT

Objective: This study aimed to identify the rheumatoid arthritis (RA) patients under biological therapy who have FRAX® scores classified as high fracture risk and to evaluate if they are receiving treatment for osteoporosis (OP). The authors also investigated the intra-individual agreement between FRAX® fracture risk calculated with and without bone mineral density (BMD).

Methods: A single-center retrospective cohort study was performed in a total of 303 patients with RA under biologics. Demographic and clinical data were collected using Rheumatic Diseases Portuguese Register (Reuma.pt), complemented with data from the hospital clinical records. FRAX scores with and without BMD were calculated. The Kendall's Tau coefficient was used to assess the agreement between FRAX risk categories. Correlations were evaluated by the Spearman test. Comparisons of distributions from independent variables used the Mann-Whitney test.

Results: When FRAX® score was calculated without BMD (n=303), 25% patients were categorized as high fracture risk. Among them, only 54% were receiving OP treatment. FRAX® assessment with BMD (n=231) identified 33% patients with high fracture risk, 52% in treatment for OP. Thirty patients (21%) previously classified as low fracture risk using FRAX® without BMD were recategorized as high risk (τ=0.570, p<0.001). Despite that, there was a strong correlation between fracture risks assessed with and without BMD.

Conclusion: The authors highlight the high number of patients, around 50%, who are not receiving treatment according to FRAX categorization. There is a discordance in fracture risk categorization, as one-fifth of low-risk patients according to FRAX without BMD were reclassified as high-risk after FRAX recalculation with BMD data, raising the need to request a dual-energy X-ray absorptiometry not only for patients classified as having an intermediate risk of fracture, but also for low-risk patients.

Keywords: DMARDs; Osteoporosis ; Rheumatoid arthritis ; Biological therapies; Bone.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial inflammation and hyperplasia, autoantibodies production, cartilage and bone destruction and systemic features, including cardiovascular, pulmonary, psychological and skeletal disorders[1]. Osteoporosis (OP) is one of the major comorbidities of RA, affecting nearly one-third of the RA population and is caused by several complex pathophysiologic processes[2, 3]. Incidence rate of fractures is 1.5 times higher in RA patients than that for the general population[4]. Bone fragility in RA results from a mix of systemic inflammation, circulating autoantibodies and pro-inflammatory cytokine secretion that collectively have deleterious effects on bone. Moreover, treatment with glucocorticoids also play a crucial role in the development of OP in RA[5]. However, despite the association of RA and OP, only about 45% of RA patients are receiving calcium and vitamin D supplements[6] and only 5.4% of RA patients who are not taking glucocorticoids are using bisphosphonates[7]. Therefore, OP screening strategies are crucial for fracture prevention in RA patients since they have unique risk factors[5].

FRAX® tool is a freely available online computer-based algorithm developed by the World Health Organization (WHO) for estimation of the 10-year risk of a hip or major osteoporotic fracture (hip, clinical

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Submitted: 14/10/2022
Accepted: 16/12/2022

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spine, humerus or wrist fracture) based on clinical risk factors[8]. These risk factors are age, gender, body mass index (BMI) and dichotomized risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, long-term oral glucocorticoid use, rheumatoid arthritis, other causes of secondary OP and daily alcohol consumption[8]. Inclusion of femoral neck bone mineral density (BMD) in the estimation is optional[8]. Fracture probability differs markedly within and across regions of the world so that FRAX® models are calibrated to the epidemiology of fracture and death in individual nations[9, 10].

The aim of this study was to identify the RA patients under treatment with biological disease-modifying antirheumatic drugs (bDMARDs) who have FRAX scores classified as high fracture risk, and to evaluate if they are receiving treatment for OP. Secondary objectives were to investigate the intra-individual agreement between FRAX fracture risk calculated with and without BMD and to explore the relationships between autoantibodies (ACPA and FR), erosive disease and FRAX fracture risk.

MATERIALS AND METHODS

Study population

Patients eligible to participate in this study were diagnosed with RA using either the American College of Rheumatology (ACR) 1987 or ACR/European League Against Rheumatism (EULAR) 2010 criteria. Demographic and clinical data from RA patients followed in a tertiary university hospital and registered in the Rheumatic Diseases Portuguese Register (Reuma.pt) were used for analysis. All patients were being treated with bDMARDs, which allowed us to study a RA population that is evaluated in a more systematic, protocolized, frequent and rigorous way, thus translating the best possible scenario in terms of care, including the realization of DXA for fracture risk stratification. Patients under 40 years of age at the last visit were excluded. The demographic data comprised age, sex, body weight, height, BMI, underlying diseases, smoking and alcohol consumption status and menopausal status. The clinical disease activity of RA was assessed using the Disease Activity Score in 28 Joints based on *c-reactive protein* (CRP) (DAS28-4V-CRP). Treatments, which included glucocorticoids, DMARDs, calcium and/or vitamin D supplements and anti-osteoporosis drugs were reviewed. In addition, evidence of previous fragility fracture (history and radiographic) and risk factors for fragility fracture based on FRAX® tool were recorded. FRAX® was calculated prior to initiation of treatment for OP, in treatment-naïve patients for OP or in patients who have discontinued bisphosphonate therapy for 2 years or non-bisphosphonate therapy for 1 year.

Osteoporotic fracture risk evaluation by FRAX® tool

The 10-year risk fracture was calculated using online FRAX® tool for the Portuguese population available at the website http://www.shef.ac.uk/FRAX. The FRAX® tool provides two results. The first is a prediction of the 10-year risk for a hip fracture, and the other is a prediction of the 10-year risk for a major osteoporotic fracture of the hip, spine, forearm or humerus. In this study, FRAX score without BMD was calculated for all patients and BMD was included when patients had performed a dual-energy X-ray absorptiometry (DXA) within the previous 6 months. When BMD was included, the manufacturer of DXA (GE-Lunar) was selected and the femoral neck BMD value entered.

Without BMD, the probability of fracture was categorized as low, moderate or high. According to the *Portuguese recommendations for the prevention, diagnosis and management of primary osteoporosis – 2018 update*, a low 10-year probability has a value less than or equal to 7 for a major osteoporotic fracture or less than or equal to 2 for a hip fracture. A high 10-year probability has a value greater than or equal to 11 for a major osteoporotic fracture or greater than or equal to 3 for a hip fracture. A moderate 10-year probability has a value between those specified for the low and high probability groups, in which case the DXA is recommended and the risk recalculated. With BMD, a high 10-year probability has a value greater than or equal to 9 for a major osteoporotic fracture or greater than or equal to 2.5 for a hip fracture[11].

Statistical Analysis

The descriptive analysis of continuous variables consisted of the mean and standard deviation (SD) for approximately symmetric distributions, and the median, maximum and minimum values otherwise. The Kendall's Tau coefficient was used to measure the agreement between risk categories. The significance of correlations was evaluated by the Spearman test. The comparison of skewed independent distributions used the Mann-Whitney test. All statistical analyses were conducted with the Statistical Package for the Social Sciences (SPSS), version 23.0 (SPSS, Chicago, IL, USA). The significance level was set at 0.005.

RESULTS

Baseline characteristics of the study participants

Three hundred and three patients with RA were enrolled from the Reuma.pt. Their baseline characteristics are shown in Table I. The mean age (SD) was 59.5 (9.5) years; mostly (80.5%) female; with an average disease

Table I. Baseline characteristics of the considered sample of RA patients under biologics.

No. of subjects	303
Clinical risk factors for osteoporosis	
Age, years (mean±SD)	59.5 ± 9.5
Weight in kg (mean±SD)	70.5 ± 13.7
Height in cm (mean±SD)	160.1 ± 8.3
Female sex, n (%)	244 (80.5)
Current smokers, n (%)	49 (16.2)
Alcohol 3U/day, n (%)	12 (4.0)
Previous fracture, n (%)	35 (11.6)
Parent hip fracture, n (%)	19 (6.3)
Secondary osteoporosis, n (%)	9 (3.0)
Exposure to oral glucocorticoids, n (%)	298 (98.3)
Rheumatoid arthritis	
Disease duration, years (mean±SD)	18.5 ± 10.4
Disease activity score (DAS28-4V-CPR) (mean±SD)	3.1 ± 1.2
RF positive, n (%)	220 (72.4)
ACPA positive, n (%)	243 (80.2)
Erosive disease, n (%)	156 (51.5)
csDMARDs, n (%)	179 (58.9)
bDMARDs, n(%)	303 (100)
BMD, g/cm²	
Femoral neck BMD, g/cm² (mean±SD)	0.8 ± 0.1
FRAX 10-year risk of major fracture (%) [median (min-max)]	
Without BMD	6.0 (1.2-50)
With BMD	6.9 (1.3-61)
FRAX 10-year risk of hip fracture (%) [median (min-max)]	
Without BMD	1,5 (0,1-40)
With BMD	1.7 (0-49)

Qualitative variables are described by their absolute (relative) frequencies while continuous variables are described by the mean (standard deviation) if approximately symmetric, or by the median (minimum-maximum) otherwise. ACPA - anti-citrullinated protein antibodies, BMD - bone mineral density, bDMARDs – biological disease-modifying antirheumatic drugs, csDMARDs - conventional synthetic disease-modifying antirheumatic drugs, RF- rheumatoid factor.

duration (SD) of 18.5 ± 10.4 years. Most of the women (91.8%) were post-menopausal, 12.1% of them in early menopause. Forty-nine patients (16.2%) were current smokers and 12 (4.0%) were alcohol consumers. The mean disease activity score (DAS28-4V-CRP) (SD) was 3.08 ± 1.18 and 174 patients (57.8%) were currently in remission or low disease activity (DAS28-4V-CRP < 3.2). Two hundred and twenty patients (72.4%) and 243 (80.2%) were rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) positive, respectively, and 156 (51.5%) had erosive disease. All patients were treated with bDMARDs (mostly tumor necrosis factor [TNF] inhibitors) and 179 (58.9%) were concomitantly treated with conventional synthetic DMARDs (csDMARDs). Ninety-eight percent have used prednisolone at some point, but 70.7% were still current users. Among all the patients, 35 (11.6%) had previous osteoporotic fractures; of these, 9 (25.7%) were a hip fracture, 8 (22.9%) a wrist fracture, 8 (22.9%) a vertebral fracture, 7 (20.0%) a humerus fracture, 2 (5.7%) a lower leg fracture and 1 (3.8%) a foot fracture. Nineteen patients (6.3%) had family history of fracture. Mean femoral neck BMD and mean T score were 0.84 ± 0.12 g/cm2 and -1.5 ± 0.9, respectively.

Fracture risk according FRAX® tool

The median 10-year risk of a major fracture and a hip fracture, without BMD, was estimated at 6.0 (1.2-50) and 1.5 (0.1-39), respectively; with BMD it was estimated at 6.9 (1.3-61) and 1.7 (0-49), respectively (Table I). FRAX® tool, calculated without BMD (n=303), determined that 59.4% (180), 15.4% (47) and 25.1% (76) of the enrolled patients had low, moderate and high 10-year probability of having osteoporotic fractures, respectively. Among patients categorized as high fracture risk, only 41 (54%) were receiving OP treatment. FRAX® assessment with BMD (n=231) identified 99 (32.7%) patients with high fracture risk, and only 51 (51.5%) were receiving OP treatment. Thirty patients (21%) previously classified as low fracture risk using FRAX®without BMD, were recategorized as high risk when BMD was included (τ=0.570, p<0.001) (Table II). Despite that, there was a strong correlation between fracture risks assessed with and without BMD for both major and hip fracture (r=0.867, p<0.0001 and r=0.728, p<0.0001, respectively).

The present study also investigated the relationship between auto-antibodies and FRAX fracture risk. ACPA and RF positive patients did not have higher 10-year probability of major or hip fracture including or not BMD (p>0.05) (Table III). Patients with erosive disease had a higher 10-year probability of major fracture evaluated by FRAX® when it includes BMD (p=0.041), but differences in 10-year probability of hip fracture was not found (p>0.05) (Table IV).

DISCUSSION

The authors found that almost half of the high-risk fracture patients according to the FRAX® categorization were not receiving OP treatment, showing the gap be-

Table II. Intra-individual agreement between FRAX fracture risk calculated with and without BMD among RA patients under biologics (τ=0.570, p<0.001)

	Low fracture risk (with BMD) n(%)	High fracture risk (with BMD) n (%)	Total
Low fracture risk (without BMD) n (%)	111 (78.7)	30 (21.3)	141
Intermediate fracture risk (without BMD) n (%)	17 (50.0)	17 (50.0)	34
High fracture risk (without BMD) n (%)	4 (7.1)	52 (92.9)	56
Total	132	99	231

BMD - bone mineral density. τ - Kendall's Tau coefficient

Table III. FRAX 10-year fracture risk and ACPA and RF in RA patients under biologics

		ACPA			RF		
		Negative Median (min-max)	Positive Median (min-max)	p value*	Negative Median |(min-max)	Positive Median (min-max)	p value*
10-year risk of major fracture (%)	without BMD	6.2 (1.6-50.0)	6.0 (1.9-49.0)	0.746	6.9 (1.9-50.0)	5.9 (1.2-49.0)	0.241
	with BMD	5.8 (2.1-31.0)	7.1 (1.3-61.0)	0.283	6.8 (2.4-61.0)	6.9 (1.3-46.0)	0.758
10-year risk of hip fracture (%)	without BMD	1.5 (0.1-39.0)	1.5 (0.1-36.0)	0.408	2.0 (0.1-39.0)	1.5 (0.1-36.0)	0.569
	With BMD	1.1 (0.0-16.0)	1.8 (0.0-49.0)	0.299	1.5 (0.0-49.0)	1.8 (0.0-29.0)	0.553

*Independent samples Man-Whitney test. BMD - bone mineral density.

Table IV. FRAX 10-year fracture risk and erosive disease in RA patients under biologics

		Erosive disease		
		Negative Median (min-max)	Positive Median (min-max)	p value*
10-year risk of major fracture (%)	without BMD	5.3 (1.2-50.0)	6.7 (1.9-44.0)	0.091
	with BMD	6.1 (1.3-46.0)	7.2 (2.1-61.0)	0.041
10-year risk of hip fracture (%)	without BMD	1.3 (0.1-39.0)	2.1 (0.2-29.9)	0.054
	With BMD	1.4 (0.0-29.0)	2.2 (0.0-49.0)	0.081

*Independent samples Man-Whitney test. BMD - bone mineral density.

tween the number of patients who are indicated for OP treatment and who are taking medication for OP. Despite the observation that patients with RA are at high risk of OP, screening is underperformed[12]. Findings from a meta-analysis including all published studies through 2017 suggest that fracture risk in RA remains high, compared to the general population[13] and a study from Spain found increasing hip fracture rates in RA population from 1999 to 2015[14]. Systematic screening of RA patients may decrease the long-term risk of fracture, as a result of increased use of anti-osteoporosis medications.

Furthermore, our results suggest that screening in RA patients under biologics should involve DXA evaluation. In spite of the strong correlation between estimated fracture risk by FRAX® with and without BMD, there is a discordance in fracture risk categorization, as one fifth of patients of low risk were reclassified as high risk when BMD was included. This indicates that the inclusion of BMD in FRAX® tool has impact on treatment categorization based on the Portuguese recommendations for OP. On the other hand, a recent study showed that despite FRAX® fracture risk estimates in individual RA patients may substantially disagree when BMD is used or not, this seems to have little impact on treatment categorization[15]. For the RA population treated with bDMARDs, our findings raise the need to request a DXA not only for patients classified as having an intermediate risk of fracture, but also for low-risk patients.

It must be considered that FRAX® tool has some limitations that may explain why RA patients under biologics may require a DXA scan. FRAX® does not take into account any RA-specific characteristics, like disease duration, disease activity, auto-antibodies positivity and erosive disease, and therefore may not accurately estimate fracture risk in this population[18, 19]. Moreover, it does not consider the dose-response factor for several risk factors (number of previous fractures, doses of glucocorticoids, smoking or alcohol) and does not include lumbar spine BMD or the number of falls[20]. A critical assessment is needed in the interpretation of the fracture risk of an individual patient with RA[12].

Currently, there are no guidelines for the prevention and treatment of OP that are specific to patients with RA. In 2022, the *Bone Health and Osteoporosis Foundation (BHOF)*[16] provide recommendations for BMD screening that can be applied to the RA population. The BHOF guidelines supports BMD screening in all adults with RA or taking a medication associated with low bone mass or bone loss (e.g. glucocorticoids). Moreover, the ACR guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis (2017)[17] recommends BMD screening for anyone age 40 and older who are taking ≥ 2.5 mg prednisone equivalents per day for 3 months or longer and provides guidance for BMD testing for those younger than 40 years with significant risk factors.

Previous studies have found conflicting results regarding the association between ACPA levels and BMD. A recent study found that ACPA positivity was associated with lower BMD at enrollment in two early RA cohorts but was not associated with an increased risk for BMD loss over time, when compared to ACPA negative patients[21]. The authors hypothesized that BMD loss was stabilized due to the tight RA disease control and reduced inflammation that was achieved in both groups. A 2019 study found ACPA level, rather than positivity, to be associated with BMD loss at the total hip, but not at the lumbar spine and forearm[22]. There are also mixed data regarding the association of RF and BMD in RA[23]. However, whether ACPA or RF positivity is associated with high risk of fracture calculated by FRAX® tool in RA patients remains unclear. *Cheng at al* found that ACPA positive RA patients had a higher 10-year probability of major or hip fracture[19]. In our study, differences in 10-year probability of major and hip fracture among patients with ACPA and/or RF positive versus negative were not found. Similar to autoantibodies, erosive disease has been shown to be associated with lower BMD[24], but the relationship with increased fracture risk has not been delineated. In our study, patients with erosive disease had a higher 10-year probability of major fracture evaluated by FRAX when it includes BMD, but differences in 10-year probability of hip fracture were not found.

One of the main limitations of our study is the retrospective nature of data, which made it difficult to correctly collect fracture risk factors. It is important to highlight that some data (such as age of menopause, history of parental fracture) were recalled data. Besides that, DXA was not available in all patients. Furthermore, the study was conducted only in patients under bDMARDs and these findings cannot be extrapolated for all RA patients.

CONCLUSION

It is imperative to accurately assess the risk of osteoporotic fractures in RA patients to treat them properly. The authors highlight the high number of patients who are not receiving treatment according to FRAX® categorization. For the RA population treated with bDMARDs, our findings raise the need to request a DXA not only for patients classified as having an intermediate risk of fracture, but also for low-risk patients. Further studies are needed to determine the real impact of our findings.

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