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ORIGINAL RESEARCH

Autoantibodies Serum Level and 10-Year Risk of Fractures Evaluated by FRAX® Tool in Rheumatoid Arthritis Patients

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Purpose: FRAX® is a tool used for evaluation of risk of fracture in RA and non-RA patients and to identify those eligible for intervention. One of the limitations of FRAX in RA settings is that it does not consider factors known to contribute to osteoporosis such as autoantibodies. This study analysed the association of anti-mutated citrullinated vimentin antibody (anti-MCV), anti-cyclic citrullinated peptide antibody (anti-CCP), IgM rheumatoid factor (RF), IgA RF with 10-year risk of major osteoporosis and hip fracture.

Methods: FRAX® tool was used to estimate 10-year risk of major osteoporosis fracture and hip fracture in 189 RA patients over 40 years of age. Anti-MCV, anti-CCP, IgM RF and IgA RF were tested using enzyme immunoassay and analysed at different levels. Results were adjusted for various confounders including disease activity.

Results: Fifty-one (26.9%) RA patients had high (≥20%) 10-year risk of major osteoporosis fracture and 67 (35.4%) had high (>3%) 10-year risk of hip fracture. Among all the tested autoantibodies, only IgM RF at elevated levels was associated with high 10-year risk of major osteoporosis fracture (adjusted OR = 4.1, 95% CI = 1.5–11.3, $p = 0.006$) and of hip fracture (adjusted OR = 17.4, 95% CI = 3.7–81.3, $p < 0.0001$). There was no agreement between FRAX and femoral neck (FN) BMD. None of the autoantibodies tested were associated with FN osteopenia or osteoporosis including IgM RF at high levels.

Conclusion: Our study highlights the importance of quantitative measurement of autoantibodies in assessment of risk for fractures among RA patients. Our preliminary findings need to be assessed in prospective studies to determine the actual predictive value of high IgM RF levels among patients with RA.

Keywords: osteoporosis, rheumatoid arthritis, 10-years risk of major osteoporosis fracture, 10-years risk of hip fracture, FRAX, anti-mutated citrullinated vimentin antibody, anti-cyclic citrullinated peptide antibody, rheumatoid factor, rheumatoid factor isotypes

Introduction

Patients with rheumatoid arthritis (RA) have reduced bone mineral density (BMD) and are at a higher risk of developing osteoporosis and fragility fractures compared with the general population.[1] Vertebral fractures are estimated to be five times more frequent in RA patients than in the general population.[2]

Several factors contribute to bone loss in RA, such as inflammation, autoimmunity, glucocorticoids, and disability. Inflammatory cells within the joints secrete pro-inflammatory cytokines and growth factors, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-17, and macrophage colony-stimulating factor (M-CSF). These cytokines play key roles in bone remodeling. They elicit osteoclast differentiation and activation, partially through receptor activator of nuclear kappa beta ligand (RANKL).[3] Pro-inflammatory cytokines act synergically to promote bone resorption and also inhibit osteoblast differentiation and activation.[4–6] The adaptive immune system also contributes to bone damage, primarily through autoantibodies.

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Approximately two-thirds of patients with RA have rheumatoid factor (RF) and anti-cyclic citrullinated protein/peptide antibodies. These autoantibodies have been associated with local bone damage[7] and low BMD.[8,9]

Treatment options, such as biologic disease-modifying anti-rheumatic drugs (bDMARDs) and synthetic targeted DMARDs, have drastically improved the prognosis of RA by preventing irreversible joint destruction. The availability of these effective drugs has prompted intense efforts to identify factors predicting local and systemic bone loss. BMD alone is insufficient to identify patients with RA who are at risk of fractures, as only half of patients with fractures have BMD ≤ -2.5 standard deviations (SD).[10] The World Health Organization (WHO) developed a fracture risk assessment tool (FRAX®) to estimate the 10-year risk of major osteoporotic and hip fractures in patients with RA over 40 years old.[11] The scoring integrates several risk factors, such as age, gender, fracture history, femoral neck (FN) BMD, and RA. The FRAX tool® is more effective in detecting patients with RA who have a greater risk of osteoporotic fractures than the WHO criteria alone.[12]

This study aimed to assess the association between the 10-year risk of major osteoporosis and hip fractures and anti-mutated citrullinated vimentin antibody (anti-MCV), anti-cyclic citrullinated peptide antibody (anti-CCP), and IgM and IgA RF isotypes.

Patients and Methods

Study Patients

In this cross-sectional study, a total of 235 adult in-patients with RA were recruited from the Department of Rheumatology of Farhat Hached University Hospital between January 2018 and December 2020. RA diagnosis was confirmed in accordance with the ACR/EULAR 2010 criteria.[13] Of the 235 recruited patients, 189 met the inclusion criteria and were enrolled in the study. To be eligible for inclusion, patients had to have a confirmed diagnosis of RA in accordance with the ACR/EULAR 2010 criteria, be aged between 40 and 90 (age of FRAX applicability) and have undergone autoantibody detection and BMD measurement prior to any osteoporosis treatment. Patients with incomplete data or who received a definitive diagnosis other than RA were excluded. Disease duration was defined as the time elapsed between the initial self-reported joint symptoms and study enrolment. Body mass index was calculated as a patient's weight in kilograms divided by their height in meters squared. Data on characteristics known to increase bone fragility, such as gender, age, menopausal status, age at menopause onset, smoking history, alcohol intake, lifestyle, comorbidities such as diabetes and dysthyroidism, and evidence of previous parental or personal fragility fractures were recorded. Details of assessment including erythrocyte sedimentation rate (ESR), C reactive protein (CRP), and 28-joint Disease Activity Score (DAS28)-ESR (https://www.das-score.nl/en/) were also retrieved. Data regarding the management of RA (cumulative dose of glucocorticoids and use of conventional synthetic DMARDs (csDMARDs) and bDMARDs) and osteoporosis regimens were collected.

This study was performed in accordance with the principles of the Helsinki Declaration and was approved by the ethics committee of Farhat Hached University Hospital. All patients provided informed consent.

Methods

Autoantibody Measurements

Serum anti-MCV, IgA RF, and IgM RF were detected using the commercially available enzyme-linked immunosorbent assay (ELISA) (Orgentec®, Hamburg, Germany). Serum anti-CCP antibody was assessed via a second-generation ELISA (Euroimmun®, Lubeck, Germany). All tests were performed in accordance with manufacturers' instructions. For the autoantibodies tested, optimal cut-off values were determined by plotting sensitivity against 1 − specificity to obtain receiver operating characteristic curves.[14,15]

BMD Assessment

FN BMD was measured using dual-energy X-ray absorptiometry (Lunar Prodigy Advance Scans, GE Healthcare, USA). Absolute BMD was computed from the bone area (cm^2) and bone mineral content (g) and expressed in grams per square centimeter (g/cm^2) and converted in *Z* score and T score. Osteopenia and osteoporosis were defined based on T score according to the WHO criteria.[16]

Ten-Year Risk of Major Osteoporosis and Hip Fractures

The 10-year risk of major osteoporosis and hip fracture scores were estimated using FRAX® based on FN BMD in g/cm^2 and several other variables, including age, sex, weight, height, smoking history, alcohol intake, previous fractures, parental hip fractures, secondary osteoporosis, corticosteroids, and RA. Because in FRAX tool, corticosteroids are entered as dichotomous variable and corticosteroids especially at high doses are well known to affect fracture probability, the 10-year risk of major osteoporosis fracture score was adjusted for corticosteroid use (adjustment coefficient was 0.8 for corticosteroids dose <2.5 mg/j, 1 for doses between 2.5 and 7.5 mg/j, and 1.15 for doses >7.5 mg/j.[17,18] The 10-year risk of major osteoporosis fracture was considered high when the score was ≥20%. The 10-year risk of hip fracture was considered high when the score was ≥3%.

Statistical Analysis

Data were checked for normality. The chi-squared test was used for dichotomous variables. The Student's *t*-test was used to compare the means of normally distributed continuous variables, while the Mann–Whitney test was used to compare the medians of non-normally distributed continuous variables. Correlations between quantitative variables were evaluated using Spearman's rank correlation coefficients. Cohen's kappa coefficient was used to measure the inter-rater reliability of the 10-year risk of major osteoporosis and hip fractures based on FN BMD. The association between the 10-year risk of fracture and autoantibodies as dichotomous variables (positive/negative) was evaluated. The significance of autoantibody levels was additionally studied by categorizing the levels into quartiles indicating low, moderate, and elevated levels.

To identify variables independently associated with a high 10-year risk of fracture, a multivariate logistic regression analysis, in which high 10-year risks of major osteoporosis and hip fractures were considered the dependent variables, was conducted. All variables with $p < 0.2$ in the univariate analysis were considered independent variables. All analyses were performed using SPSS software 21.0. The level of significance was set at $p \leq 0.05$.

Results

Study Population (Table 1)

Overall, 189 patients with RA were included in the study. This sample included 162 (85.7%) females, of whom 140 (86.4%) were post-menopausal. The mean age of the patients was 58 ± 15. Thirty-two (16.9%) patients had early-stage RA (≤12 months) and the median (interquartile [IQR]) disease duration was 72 months (24–144 months). Most of patients had an active disease, with a median (IQR) DAS of 5.7 (4.7–6.7). One-hundred ten (58.2%) patients had extraarticular manifestations (EAM): 39 (20.6%) had respiratory EAM, 33 (17.4%) had sicca symptoms, 22 (11.6%) had

Table 1 RA Patients' Characteristics

Variable	Value
Females, n (%)	162 (85.7)
Age, mean (±SD), years	58.3 (±15.4)
Body mass index, median (IQR), kg/m^2	27.8 (22.9–32.1)
Disease duration, median (IQR), months	72 (24–144)
Extraarticular manifestations	110 (58.2)
Corticosteroids, n (%)	188 (99.4)
Corticosteroids cumulative dose, median (IQR), mg	15135 (3112–29,500)
csDMARDs, n (%)	178 (94.6)
bDMARDs, n (%)	23 (0.12)
Erythrocyte sedimentation rate, mean (SD), mm/1h	48.5 (27.5–75)
C reactive protein, median (IQR), mg/l	19.5 (8–47)
Disease activity score in 28 joints, median (IQR)	5.7 (4.7–6.7)
Anti-MCV, median (IQR), RU/mL, % of positive	372 (14–610), 72.0
Anti-CCP, median (IQR), RU/mL, % of positive	112 (45–200), 79.7

(*Continued*)

Table 1 (Continued).

Variable	Value
IgM RF, median (IQR), IU/mL, % of positive	270 (100–500), 69.8
IgA RF, median (IQR), IU/mL, % of positive	150 (70–478), 59.7
Femoral neck BMD, median (IQR) g/cm^2	0.798 (0.716–0.889)
Femoral neck *Z* score$^+$, median (IQR), SD	−1.0 (−1.5- −0.3)
Femoral neck T score^{++}, median (IQR), SD	−1.8 (−2.5- −1.0)
10- year Major osteoporosis fracture risk, median (IQR), %	13.8 (8.8–20.7)
10- year hip fracture risk, median (IQR), %	2.0 (0.9–3.9)

Notes: $^+$Femoral neck *Z* score in patients younger than 50, $^{++}$femoral neck T score in patients older than 50.

Abbreviations: SD, standard deviation; IQR, interquartile; csDMARDS, conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs; MCV, mutated citrullinated vimentin; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; BMD, bone mineral density.

nodules, 8 (4.2%) had cardiovascular EAM, 4 (2.1%) had Sjogren's syndrome, 2 (1.0%) had renal EAM, and 2 (1.0%) had vasculitis. One-hundred eighty (99.4%) patients were being treated with corticosteroids, with a median (IQR) cumulative dose of 15,135 mg (13,112–29,500 mg). One hundred and seventy-eight (94.1%) patients were being treated with csDMARDs and 23 (2.1%) with bDMARDs.

The median (IQR) 10-year risk of major osteoporosis and hip fracture scores were 13.8% (8.8–20.7%) and 2% (0.9–3.9%), respectively. Fifty-one (26.9%) patients had a high 10-year risk of major osteoporosis fractures, while 67 (35.4%) had a high 10-year risk of hip fractures.

Patients with RA who had high 10-year risks of major osteoporosis and hip fractures were older and had higher CRP values than those who had low 10-year risks (Tables 2 and 3). Ninety (47.6%) patients had FN osteopenia and 48 (25.3%)

Table 2 Characteristics of Patients with High and Low 10-Year Risk of Major Osteoporosis Fracture

Variable	Low 10-Year Risk (n=138)	High 10-Year Risk (n=51)	*P**	*p* **
Females, n (%)	115 (83.3)	47 (92.1)	-	0.1
Age, mean (SD), years	55.5 (7.5)	64.1 (9.7)	*<0.0001*	-
Body mass index, median (IQ), kg/m^2	28.1 (23.4–32.5)	26.0 (21.9–31.6)	0.1	-
Disease duration, median (IQR), months	72 (24–144) 26/135	78 (17–168)	0.8	0.1
Corticosteroids, n (%)	138 (100)	41 (80.3)	-	0.5
Corticosteroids cumulative dose, median (IQR), mg	18237 (2300–29,200)	10,800 (3650–25,287)	0.1	-
csDMARDs, n (%)	126 (91.3)	46 (90.1)	-	0.5
bDMARDs, n (%)	15 (10.8)	8 (15.6)	-	0.3
Erythrocyte sedimentation rate, mean (SD), mm/1h	48 (25–72)	50 (31–82)	0.7	-
C reactive protein, median (IQR), mg/L	18 (6–43)	30 (14–53)	*0.007*	-
Disease activity score in 28 joints, median (IQR)	5.7 (4.4–6.7)	5.9 (5.1–6.6)	0.41	-
Anti-MCV, median (IQR), RU/mL, % of positive	160 (17–569), 74.0	126 (9–750), 65.7	0.7	0.3
Anti-CCP, median (IQR), RU/mL, % of positive	90 (10–200), 77.3	96 (39–200), 86.2	0.9	0.1
IgM RF, median (IQR), IU/mL, % of positive	220 (107–420), 67.4	207 (100–500), 76.7	0.1	0.2
IgM RF≥ 500 UI/mL, n (% of positive)	17 (20.4), 20.4	15 (46.8), 46.8	-	*0.005*
IgA RF, median (IQR), IU/mL, % of positive	115 (60–456), 52.8	245 (102–500), 79.0	0.1	*0.003*
Femoral neck BMD, median (IQR) g/cm^2	0.817 (0.747–0.944)	0.764 (0.651–0.825)	*0.009*	-
Femoral neck *Z* score$^+$, median (IQR), SD	−0.9 (−1.5–0.0)	−1.0 (−1.7- −0.4)	0.9	-
Femoral neck T score^{++}, median (IQR), SD	−1.5 (−2.3- −0.6)	−2.1 (−3.1- −1.6)	*0.004*	-
Femoral neck osteopenia, n (%)	63 (45.6)	27 (51.9)	-	0.3
Femoral neck osteoporosis, n (%)	28 (20.2)	20 (39.2)	-	*0.008*
10-year risk of hip fracture, median (IQR), %	1.2 (0.7–2.2), 14.4	7.4 (4.2–12.0), 92.1	*<0.0001*	*<0.001*

Notes: $^+$Femoral neck *Z* score in patients younger than 50, $^{++}$femoral neck T score in patients older than 50, *significance of mean/median comparison tests, **significance of Chi squared test for proportions' comparison. Italic values are statistically significant.

Abbreviations: SD, standard deviation; IQR, interquartile; csDMARDS, conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs; MCV, mutated citrullinated vimentin; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; BMD, bone mineral density.

Table 3 Characteristics of Patients with Low and High 10-Year Risk of Hip Fracture

Variable	Low 10-Year Risk (n=122)	High 10-Year Risk (n=67)	*p**	*p***
Females, n (%)	104 (85.2)	58 (86.5)	-	0.8
Age, mean (SD), years	53.4 (6.8)	64.9 (7.9)	*<0.0001*	-
Body mass index, median (IQ), kg/m^2	28.1 (23.5–32.4)	27.1 (22.2–31.8)	0.3	-
Disease duration, median (IQR), months	72 (24–144)	66 (17–144)	0.9	0.9
Corticosteroids, n (%)	122 (100)	66 (98.5)	-	0.1
Corticosteroids cumulative dose, median (IQR), mg	17872 (1950–28,975)	10,975 (3650–31,481)	0.3	-
csDMARDs, n (%)	110 (90.1)	62 (92.5)	-	0.3
bDMARDs, n (%)	13 (10.6)	10 (14.9)	-	0.3
Erythrocyte sedimentation rate, mean (SD), mm/1h	48 (25–70)	51 (34–94)	0.2	-
C reactive protein, median (IQR), mg/L	16 (6–44)	27 (14–50)	*0.01*	-
Disease activity score in 28 joints, median (IQR)	5.6 (4.3–6.6)	5.9 (5.2–6.8)	0.3	-
Anti-MCV, median (IQR), RU/mL, % of positive	165 (17–542), 73.4	126 (9–710), 69.3	0.7	0.6
Anti-CCP, median (IQR), RU/mL, % of positive	90 (10–200), 78.5	96 (36–200), 82.0	0.9	0.5
IgM RF, median (IQR), IU/mL, % of positive	190 (88–402), 68.5	445 (112–500), 72.4	0.1	0.6
IgM RF≥ 500 UI/mL. n (% of positive)	13 (17.5), 17.5	19 (46.3), 46.3	-	*0.001*
IgA RF, median (IQR), IU/mL, % of positive	111 (60–437), 51.8	245 (87–500), 74.1	0.084	*0.005*
Femoral neck BMD, median (IQR) g/cm^2	0.829 (0.769–0.944)	0.752 (0.654–0.813)	*<0.0001*	-
Femoral neck *Z* score$^+$, median (IQR), SD	−1.0 (−1.6--0.1)	−0.7 (−1.3--0.4)	0.6	-
Femoral neck T score^{++}, median (IQR), SD	−1.4 (−2.0- −0.6)	−2.1 (−3.0- −1.6)	*<0.0001*	-
Femoral neck osteopenia, n (%)	62 (50.8%)	28 (41.7)	-	0.2
Femoral neck osteoporosis, n (%)	18 (14.7)	30 (44.7)	-	*<0.0001*
10-year risk of major osteoporosis fracture, median (IQR), %	11.0 (4.0–14.9), 3.2	24.1 (19.5–32.2), 70.1	*<0.0001*	*<0.0001*

Notes: $^+$Femoral neck *Z* score in patients younger than 50, $^{++}$femoral neck T score in patients older than 50, *significance of mean/median comparison tests, **significance of Chi squared test for proportions' comparison. Italic values are statistically significant.

Abbreviations: SD, standard deviation; IQR, interquartile; cDMARDS, conventional disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs; MCV, mutated citrullinated vimentin; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; BMD, bone mineral density.

had FN osteoporosis. The agreement between the 10-year risk of major osteoporosis fracture and FN osteopenia or osteoporosis was 0.05 and 0.19, respectively. The agreement between the 10-year risk of hip fracture and FN osteopenia or osteoporosis was −0.08 and 0.32, respectively.

The anti-MCV antibody was detected in 103 (72%) of the 143 patients tested, while anti-CCP was detected in 150 (79.7%) of the 188 patients tested. Both anti-MCV and anti-CCP were detected in 88 (59%) patients out of 149. IgA RF was detected in 98 (59.7%) of 164 patients, while IgM RF was detected in 116 (69.8%) of 166 patients tested. Both IgA RF and IgM RF were detected in 88 (53.6%) patients out of 164. IgM RF levels were available for 115 patients. Thirty-two (27.8%) patients had elevated IgM RF levels (≥ third quartile = 500 UI/mL).

Association Between Autoantibody Levels, 10-Year Fracture Risk, and Low FN BMD

Univariate Analysis

Tables 2 and 3 show the different autoantibody levels in patients with RA who had high or low 10-year risks of fractures. High levels of IgM RF (≥500 UI/mL) were associated with a high 10-year risk of major osteoporosis fractures (OR = 3.4, 95% CI = 1.4–8.2, p = 0.005) and hip fractures (OR = 4.0, 95% CI = 1.7–9.5, p = 0.001). The 10-year risk of major osteoporosis fracture scores were higher in patients with high levels of IgM RF than in patients with lower IgM RF levels (<500 UI/mL). However, the difference was not statistically significant (17.5% [7.6–24.0%] versus 11% [6.9–17.0%], p = 0.8). Likewise, the 10-year risk of hip fracture scores were higher in patients with high IgM RF levels than in patients with low IgM RF levels. However, this difference was also not statistically significant (3.8% [0.7–6.4%] versus 1.5% [0.8–3.1], p = 0.1). Even at high levels, IgM RF was not associated with FN osteopenia (OR = 0.7, 95% CI = 0.3–1.4, p = 0.3) or FN osteoporosis (OR = 1.2, 95% CI = 0.5–2.5, p = 0.5).

IgA RF levels were associated with a high 10-year risk of major osteoporosis fractures (OR = 3.3, 95% CI = 1.4–7.6, p = 0.003) and hip fractures (OR = 2.6, 95% CI = 1.3–5.3, p = 0.005). However, they were not associated with FN

osteopenia (OR = 0.7, 95% CI = 0.4–1.4, $p = 0.4$) or osteoporosis (OR = 1.12, 95% CI = 0.5–2.3, $p = 0.5$). All 54 (62%) patients who demonstrated high IgM RF levels also harbored IgA RF. To disentangle the impact of these antibodies on the 10-year risk of major osteoporosis and hip fractures, we assessed the association between IgA RF levels and a high 10-year risk of major osteoporosis or hip fractures in patients with low IgM RF levels (<500 UI/mL). No association was found with major osteoporosis (OR = 1.7, 95% CI = 0.4–5.8, $p = 0.3$) or hip fractures (OR = 1.3, 95% CI = 0.4–4.0, $p = 0.5$). Anti-MCV, anti-CCP, and coexisting anti-MCV and anti-CCP levels were not associated with the 10-year risk of major osteoporosis or hip fractures or with FN osteopenia or osteoporosis (data not shown).

Multivariate Analysis (Table 4)

Of the variables with $p < 0.2$ that were integrated into the multivariate analysis, only high levels of IgM RF (adjusted OR for major osteoporosis fractures = 4.1, 95% CI = 1.5–11.3, $p = 0.006$; adjusted OR for hip fractures = 17.4, 95% CI = 3.7–81.3, $p < 0.0001$) and age (adjusted OR for major osteoporosis fractures = 1.1, 95% CI = 1.0–1.2, $p < 0.0001$; adjusted OR for hip fractures = 1.3, 95% CI = 1.1–1.5, $p < 0.0001$) were identified as independent 10-year risk factors for fractures.

Discussion

Our data showed that, unlike anti-CCP, anti-MCV, and IgA RF levels, high IgM RF levels and age were independently associated with a high 10-year risk of major osteoporosis and hip fractures. To the best of our knowledge, this is the first study to analyze the relationship between anti-MCV and IgA RF levels and the 10-year risk of fracture estimated using FRAX® in patients with RA.

RF is a polyclonal autoantibody against the Fc region of IgG. The 2010 ACR/EULAR RA classification considers the presence of RF and ACPA to be classification criteria for RA.[13] RF is not specific to RA; however, the simultaneous increase in IgA RF and IgM RF, which is the most common RF pattern found in patients with RA, is rarely found in non-RA patients.[19] The 2010 ACR/EULAR classification criteria do not require a specific RF isotype for RA classification. Most clinical laboratories globally use turbidimetric and nephelometric assays for RF detection. These assays are not isotype-specific; however, they primarily detect IgM RF. The direct effect of RF on osteoclastogenesis and cytokine production remains unknown. By forming IgG immune complexes (possibly with ACPA), RF might stimulate diverse immune cells and activate the complement. Data suggests that signaling through FcγR might activate osteoclastogenesis.[20] Moreover, RF potentiates the impact of ACPA on complement activation and macrophages, influencing the production of pro-inflammatory cytokines.[21,22]

Our study showed that at elevated levels, IgM RF was associated with a high 10-year risk of fracture, and this effect was independent of age and disease activity. In a 3-year prospective longitudinal study, reactive and non-reactive RF were not found to be risk factors for fragility fractures in patients with RA.[23] Senosi et al[24] found that FRAX® scores were higher in patients who harbored RF. However, the proportions of patients with RA who harbored RF and had a high (≥20%) 10-year risk of major osteoporosis fractures and a high (≥3%) 10-year risk of hip osteoporosis fractures were not compared with the proportions of patients negative for RF who also had high 10-year fracture risks.

Table 4 Factors Associated with High 10-Year Risk of Major Osteoporosis Fracture and Hip Fracture in the Multivariate Analysis

High 10-Year Risk of Major Osteoporosis Fracture	Adjusted OR (95% CI)	*p*
High levels of IgM RF	4.1 (1.5–11.3)	*0.006*
Age	1.1 (1.0–1.2)	*< 0.0001*
High 10-year risk of major hip fracture		
High levels of IgM RF	17.4 (3.7–81.3)	*< 0.0001*
Age	1.3 (1.1–1.5)	*< 0.0001*

Abbreviations: OR, odd ratio; CI, confidence interval.

IgA RF accumulation predates RA onset by several years and has predictive value for RA development[25] and is highly specific for RA.[26,27] In vitro, IgA immune complexes promote IL-6 and IL-8 production and enhance osteoclast-mediated bone resorption.[28] In patients with early-stage RA, IgA RF is associated with bone erosion.[29–31] Our univariate analysis demonstrated that IgA RF was associated with a high 10-year risk of fracture. However, this association did not persist in the multivariate analysis, confirming that the initial association was due to concomitantly elevated IgM RF levels.

RA is an autoimmune disease characterized by the loss of tolerance to post-translational modified proteins, such as citrullinated proteins. Vimentin is an intermediate filament involved in immune cell migration, extravasation, homing, and target recognition. It also regulates the secretion of proinflammatory cytokines, such as IL-1β and IL-18, through the NLRP3 inflammasome.[32] Citrullinated vimentin is presented by the shared epitope, a group of alleles tightly linked to genetic susceptibility to RA.[33] Anti-MCV is a sensitive marker for RA.[14,34] In mice, anti-MCV triggers significant periarticular bone loss independently of inflammation.[35] Several studies have assessed the association between anti-MCV with erosion and its prognostic value for radiographic progression in patients with RA; however, results have been conflicting.[36–38] We did not find any association between anti-MCV and the 10-year risk of fractures. To the best of our knowledge, this association has not been previously examined. We did not observe any association between anti-MCV and low FN BMD, which was in line with the results of a previous study.[39]

Anti-CCP antibodies have been associated with bone erosion and low BMD in patients with RA.[9,40–42] We did not find any association between anti-CCP levels (alone or in combination with anti-MCV levels) and the 10-year risk of fractures. Cheng et al reported higher FRAX scores in patients with RA who were positive anti-CCP than those who were negative.[43] However, the proportions of anti-CCP-positive and negative patients with RA who had high (≥20%) 10-year risks of major osteoporosis fractures and high (≥3%) 10-year risks of hip osteoporosis fractures were not compared.

In our study, there was no substantial association between FRAX scores and BMD. Furthermore, none of the antibodies tested were associated with FN osteoporosis or osteopenia. These findings corroborate the lack of correlation between FRAX scores and BMD that has been previously reported.[12,44]

Most patients had established RA. They were hospitalized at the time of study enrollment due to active disease. In Tunisia, access to bDMARDs is limited and most of our patients were being treated with high doses of corticosteroids. Therefore, we adjusted for confounding variables, such as age, disease duration, and disease activity. In Tunisia, access to bDMARDs is limited and most of our patients were being treated with high doses of corticosteroids. Because corticosteroids are known to decrease BMD and to affect fracture probability,[45,46] we integrated the cumulative dose of corticosteroids in the multivariate analysis as a possible confounding variable. Moreover, the 10-year risk of fracture score was adjusted for corticosteroid use.

The present study was limited by its cross-sectional design. Because the FRAX® tool is only relevant for patients over 40 years old, it was not possible to assess the relationship between autoantibodies and the 10-year risk of fractures in younger patients with RA. In addition, treatments can modulate autoantibody levels and possibly induce biases in serological analysis.

Conclusion

This study demonstrated an association between elevated IgM RF levels and a high 10-year risk of major osteoporosis and hip fractures. These results highlight the importance of taking quantitative autoantibody measurements during the assessment of osteoporosis-related fracture risk in patients with RA. The association of high Ig MRF levels with a higher risk of fractures needs to be assessed in long-term follow-up studies to determine the actual predictive value of high IgM RF levels among patients with RA.

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Disclosure

The authors declare that they have no competing interests in this work.

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