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Evaluation of fracture risk in Egyptian rheumatoid arthritis patients by the Fracture Risk Assessment Tool

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Abstract

Background: Rheumatoid arthritis (RA) patients have a risk of fractures due to secondary osteoporosis. This study aimed to evaluate the probability of fractures in the next 10 years in Egyptian RA patients by the Fracture Risk Assessment Tool (FRAX).

Results: The study was a case–control study. It included a hundred RA patients as well as 51 apparently healthy volunteers. Bone mineral density (BMD) means of lumbar vertebra, femoral neck, and total femur were significantly lower in the RA patient group. Additionally, FRAX of the major osteoporotic and hip fractures means were significantly higher in the RA group than in the control group. It was also found that age, body mass index (BMI), Health Assessment Questionnaire Disability Index (HAQ-DI), and BMD of the femoral neck were significant predictors of FRAX of major osteoporotic and hip fractures ($P \leq 0.05$). The cumulative dose of steroids was a significant predictor for FRAX of major osteoporotic fractures; however, the 28 joints disease activity score calculated with erythrocyte sedimentation rate (ESR) (DAS28-ESR) was a significant predictor for FRAX of hip fractures.

Conclusions: RA patients have a high fracture risk probability. Regular annual screening for BMD and FRAX of major osteoporotic and hip fractures is necessary for those patients.

Keywords: Rheumatoid arthritis, Fracture Risk Assessment Tool, Dual-energy X-ray absorptiometry, Bone mineral density

Background

Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease affecting mainly the joints. It affects about 5 per 1000 adults worldwide. It presents in ladies two to multiple times more than men and happens at any age [1]. Previously, RA prompted disability and failure to work and expanded mortality. The understanding of RA pathophysiology influenced better disease outcomes and the development of novel therapies [2].

Osteoporosis is an extraarticular complication in RA. It may be caused by inflammatory processes or glucocorticoid use. It was known that bone resorption is increased in RA due to overexpression of proinflammatory cytokines [3]. Additionally, bone formation is troubled in RA patients. The Wnt signaling pathway inhibitors, as dickkopf-1 and sclerostin, are upregulated in active RA and lead to osteoblast apoptosis that can affect bone formation. In addition, the increased activation for receptor activator of nuclear kappa B ligand (RANKL) inhibits osteoprotegerin (OPG), which leads to a prolonged lifespan of osteoclasts [4].

Systemic bone loss leads to osteoporosis with an increased risk of fragility fractures in RA patients. The bone loss seems to start early in disease development and, in some patients, even before the clinical onset of RA [5]. It was reported that RA patients had diminished bone mineral density (BMD) in the lumbar spine, hip, and whole body. The overall frequency of osteoporosis

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was double in the RA patients compared with the healthy population [6]. Other studies reported that RA patients have a high risk of fractures [7, 8].

This study aimed to assess the probability of major osteoporotic and hip fractures in the next 10 years in Egyptian RA patients using the Fracture Risk Assessment Tool (FRAX) and its relationship with disease activity and functional disability.

Methods

Patients

All subjects in the study were aged 40 years or older (as FRAX is not applicable for those younger than 40. It is validated to be applicable to both women and men aged 40 to 90 years [9]). The study was a case–control study on 100 RA patients and 51 healthy volunteers (from June 2019 to April 2020) in Physical Medicine, Rheumatology, and Rehabilitation Department. The studied RA patients met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for the classification of RA [10]. Subjects diagnosed with liver diseases, renal diseases, hypoparathyroidism, hypogonadism, secondary osteoporosis, type 1 diabetes mellitus [11], hyperthyroidism [12], malignancies, or overlap syndromes were excluded. Also, smokers and alcoholics were excluded.

Ethics approval and consent to participate

The Ethical Committee Board of Faculty of Medicine, Suez Canal University, approved this study. The reference number is 3086/10-5-2019. Written informed consent was taken from all subjects before participating in this study.

Methods

All subjects underwent entire history, clinical examination, and measurements like height and weight for body mass index (BMI) assessment [13]. The history included current medications, including disease-modifying antirheumatic drugs (DMARDs), biologics, glucocorticoids (GCs), and others as calcium, vitamin D, or antiresorptive drugs. It also included menstrual history, smoking history, alcohol intake, chronic illnesses, and regular exercise.

GC history included the dose, duration of use, and the doses last 100 days to calculate the cumulative steroid dose that was calculated by dividing the dose of steroids by the weight in each period and adding the results in the studied period, which was 100 days [14].

Functional disability assessment

Health Assessment Questionnaire Disability Index (HAQ-DI) was used for the assessment of functional disability. HAQ-DI is a dependable self-reported questionnaire covering 20 items in eight domains related to measuring difficulty in performing daily activities like arising, eating, walking, dressing, hygiene, reach, grip, and ordinary daily activities. The HAQ-DI calculator was used to measure the HAQ-DI to shape a score between zero (no disability) and 3 (extreme disability) [15].

Laboratory investigations

Serum calcium and phosphorous were measured in all participants by spectrophotometric methods. Besides this, RA patients had an evaluation of the erythrocyte sedimentation rate (ESR) (using the Westergren method (mm/h)), rheumatoid factor (RF) (considered positive if it is > 20 IU/ml), and C-reactive protein (CRP) (using the nephelometric method). The RA disease activity was measured by the 28 joints Disease Activity Score calculated with ESR (DAS28-ESR) and the 28 joints Disease Activity Score calculated with CRP (DAS28-CRP) using 28 joints Disease Activity Score (DAS28) calculator [16].

BMD measurement

All subjects in both groups had a BMD assessment by Dual-energy X-ray absorptiometry (DEXA) (GE Lunar densitometer, Madison, WI 53717-1915, USA). The measurements have been carried out within the spine from the second to fourth Lumbar vertebra, femur, and radius utilizing popular tool techniques and matched gender, weight, and race. All BMD measurements had been in grams per square centimeter.

According to the World Health Organization (WHO) criteria, osteoporosis was diagnosed when the T score was − 2.5 standard deviation (SD) or lower. Also, osteopenia diagnosis was made when the T score was lower than − 1 and higher than − 2.5 SD [17]. The T score–based WHO criteria cannot be applied to premenopausal women and should not be used to categorize such women into normal, osteopenic, or osteoporotic groups. Furthermore, since the relationship between T scores and fracture risk in premenopausal women is less clear than in postmenopausal women, a conservative approach was needed to arrive at a diagnosis even with low bone density to avoid unnecessary treatment [18]. The International Society for Clinical Densitometry (ISCD) recommended the Z scores than T scores in the osteoporosis definition in premenopausal women and men younger than 50 [19, 20]. Low bone mass for age or osteoporosis was confirmed when the Z score was less than − 2.0 SD in the presence of secondary cause for osteoporosis as RA. So, the premenopausal women and men younger than 50 in both groups were classified according to BMD into osteoporosis and normal BMD [18].

FRAX calculation

FRAX is a computer-based algorithm (http://www.shef.ac.uk/FRAX) developed by the WHO Collaborating Centre for Metabolic Bone Diseases and first released in 2008. The algorithm, intended for primary care, calculates fracture probability from easily obtained clinical risk factors in men and women [21]. The output of FRAX was the 10-year probability of a major osteoporotic fracture (hip, clinical spine, humerus, or wrist fracture) and the 10-year probability of hip fracture [9]. Probability was calculated from age, sex, BMI, and dichotomized risk factors comprising prior fragility fractures, parental history of hip fracture, current tobacco smoking, ever use of long-term oral glucocorticoid use, and high alcohol consumption. FRAX of hip fracture was considered high if it was more than or equal to 3; FRAX of major osteoporotic fractures was deemed to be high if it was more than or equal to 20 [9].

The National Osteoporosis Foundation (NOF) for the USA and the National Osteoporosis Guideline Group (NOGG) for the UK stated that patients with osteopenia (T score between − 1.0 and − 2.5 SD at the femoral neck, total hip, or spine) should be treated when there is a 10-year probability of hip fracture that is ≥ 3% or a 10-year probability of a major osteoporosis-related fracture that is ≥ 20% [22].

No FRAX calculator was available in Egypt. Using the FRAX calculator of a surrogate country is possible in such conditions [23]. The Jordan FRAX calculator was used to calculate the 10-year fracture probability for all subjects in both groups.

Statistical analysis

All the data from history, clinical examination, and investigations were coded and imported into the Statistical Package for the Social Sciences (SPSS version 25) software. The data normality of the distribution was evaluated first. All studied variables were expressed as means and standard deviations. Mann–Whitney U test, chi-squared test, and Spearman correlation coefficients explained the study results as the results were not normally distributed. Multiple linear regression analysis was used to check and estimate the dependence of a quantitative variable to set dating with a set of independent variables. The results were considered significant if P was ≤ 0.05.

Results

The data of both groups, including demographic and clinical characteristics, were listed in Table 1. The female patients were higher than males in both groups. Both groups had no significant differences regarding age, gender, BMI, and the percentage of the premenopausal to the postmenopausal women.

Significant differences were noticed regarding the means of HAQ-DI, BMD (femoral neck, total femur, and lumbar spine), and FRAX of both hip and major osteoporotic fractures between both groups (Fig. 1). There were significant differences between the study and the control group in premenopausal and postmenopausal women regarding BMD classification into normal, osteopenia, and osteoporosis. The RA patients have an increased risk of hip fractures (FRAX of hip more than or equal to 3) and major osteoporotic fractures (FRAX of major fractures more than or equal 20) in comparison with the control group (Table 1).

Age, menopausal years, HAQ-DI, cumulative steroid dose, disease duration, and FRAX of hip fractures and major osteoporotic fractures were negatively correlated to the BMD at the femoral neck and lumbar spine in the RA group. Also, DAS28-ESR and DAS28-CRP had significant negative correlations with BMD at the femoral neck. At the same time, BMI had a significant positive correlation with the BMD of the femoral neck and lumbar spine (Table 2).

The correlation analysis of FRAX and the studied variables in the RA patients revealed that FRAX of hip and major osteoporotic fractures was correlated positively to age, menopausal years, cumulative steroid dose, DAS28-ESR, DAS28-CRP, and HAQ-DI. Also, there were significant negative correlations of the FRAX of hip and major osteoporotic fractures with BMI and BMD of total femur, femoral neck, and lumbar spine (Table 3) (Figs. 2 and 3).

In multiple linear regression analysis models, it was detected that age, BMI, HAQ-DI, DAS28-ESR, and BMD at the femoral neck were significant predictors of FRAX of hip fractures. However, age, BMI, menopausal years, cumulative steroid dose, HAQ-DI, and BMD at the femoral neck were predictors of FRAX of major osteoporotic fractures (Table 4).

Discussion

RA is a chronic inflammatory joint disease. It leads to localized and generalized bone loss and eventually osteoporosis. Localized or periarticular osteoporosis is caused by cytokines and growth factors that regulate reciprocal interactions between osteoblasts, osteoclasts, and immune cells. The synoviocytes of fibroblast and macrophage phenotype, antigen-presenting cell, lymphocytes, plasma cells, and neutrophils accumulated in the inflamed joints activate RANKL that cause osteoclast activation and bone loss [4]. RA patients have a generalized osteoporosis risk that increases the risk of osteoporotic fractures, which FRAX assesses. Generalized

Table 1 Clinical and demographic characteristics in both groups

	RA group ($n = 100$)	Control group ($n = 51$)	*P* value
Age in years (*mean* ± SD)	54.65 ± 11.35	53 ± 10.6	0.343[1]
Females (%)	92 (92%)	45 (88.2%)	0.527[2]
Males (%)	8 (8%)	6 (11.76%)	
BMI (kg/m^2) (*mean* ± SD)	29.51 ± 6.81	29.518 ± 6.890	0.126[1]
Postmenopausal women (%)	44 (44%)	22 (43.1%)	0.919[2]
Premenopausal women (%)	48 (48%)	23 (45.09%)	
Premenopausal normal BMD (%)	26(54.1%)	23 (100%)	**0.032[2]**
Premenopausal osteoporosis (%)	22 (45.8%)	0 (0%)	
Postmenopausal normal BMD (%)	12 (27.27%)	7 (31.8%)	**0.045[2]**
Postmenopausal osteopenia (%)	14 (31.8%)	10 (45.45%)	
Postmenopausal osteoporosis (%)	18 (40.9%)	5 (22.7%)	
Men (< 50 years) normal BMD	5 (62.5%)	6 (100%)	0.091[2]
Men (< 50 years) osteoporosis	3 (37.5%)	0	
Postmenopausal women menopausal years (*mean* ± SD)	5.818 ± 3.500	5.5 ± 2.84	0.943[1]
Disease duration (*mean* ± SD)	6.12 ± 5.02		
RA patients on MTX (%)	47 (47%)		
RA patients on leflunamide (%)	53 (53%)		
RA patients on MTX and leflunamide compination (%)	37 (37%)		
Current use of steroids (%)	74 (74%)		
Cumulative steroid dose	20.57 ± 5.057		
Serum calcium (*mean* ± SD)	8.32 ± 0.56	8.167 ± .299	0.310[1]
Serum phosphorus (*mean* ± SD)	3.63 ± .815	3.325 ± 0.351	**0.002[1]**
RF positivity (%)	68 (68%)		
HAQ-DI (*mean* ± SD)	0.80 ± 0.497	0.176 ± 0.185	**< 0.0001[1]**
DAS28-ESR (*mean* ± SD)	4.9 ± 1.4		
DAS28-CRP (*mean* ± SD)	4.1 ± 1.4		
Low disease activity (%)	18 (18%)		
Moderate disease activity (%)	45 (45%)		
High disease activity (%)	37 (37%)		
Previous fragility fractures (%)	34 (34%)	8 (15.68%)	**0.033[2]**
Parental hip fractures (%)	20 (20%)	5 (9.8%)	0.15[2]
BMD at femoral neck in gm/cm^2	0.918 ± 0.171	1.161 ± 0.262	**< 0.0001[1]**
BMD at lumbar spine in gm/cm^2	1.03096 ± 0.221	1.197 ± 0.306	**0.004[1]**
BMD at total femur in gm/cm^2	0.92038 ± 0.185	1.180 ± 0.331	**< 0.0001[1]**
Osteoporosis of lumbar spine (%)	32 (32%)	3 (5.88%)	**0.001[2]**
Osteoporosis of femur (%)	16 (16%)	5 (9.8%)	
Osteoporosis of both lumbar spine and femur (%)	5 (5%)	3 (5.88%)	
FRAX of hip (*mean* ± SD)	1.7640 ± 2.98942	0.380 ± 0.812	**< 0.0001[1]**
FRAX of major fractures (*mean* ± SD)	5.304 ± 5.63921	2.168 ± 2.401	**< 0.0001[1]**
FRAX of hip ≥ 3 (%)	16 (16%)	2 (3.9%)	**0.042[2]**
FRAX of major fractures ≥ 20 (%)	12 (12%)	0 (0%)	**0.011[2]**
FRAX of major fractures ≥ 20 in postmenopausal women only (%)	10 (22.7%)	0	**0.048[2]**
FRAX of hip ≥ 3 in postmenopausal women only (%)	14 (31.81%)	2 (9.09%)	0.066[2]

All values are expressed in mean ± standard deviation (SD) unless otherwise noted

[1] Mann Whitney U test; [2]Chi-square test

Statistically significant at P ≤ 0.05; RA rheumatoid arthritis, *BMI* body mass index, *DMARDS* disease-modifying antirheumatic drugs, *RF* rheumatoid factor, *HAQ-DI* Health Assessment Questionnaire Disability Index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28-ESR* 28 joints disease activity score calculated with ESR, *DAS28-CRP* 28 joints disease activity score calculated with CRP, *BMD* bone mineral density, *FRAX* fracture risk assessment for 10 years fracture probability

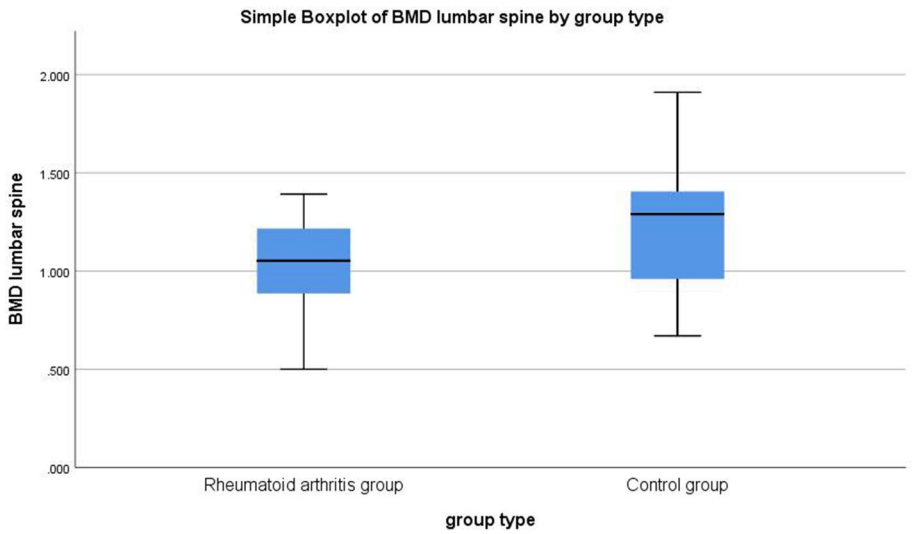

Fig. 1 BMD of the lumbar spine (in gm/cm^2) mean was lower significantly in the RA group in comparison with the control ($P = 0.004$)

bone loss may be linked to disease itself or other factors related to osteoporosis [24–26].

Multiple studies were done on BMD assessment in RA patients in various populations [6, 27–29], but no one studied it in Egyptian RA patients. Few studies assessed fracture risk in RA patients using the FRAX tool [30, 31]. This study evaluated BMD and 10-year fracture risk in Egyptian RA patients using the FRAX tool compared with a control group. The frequency of osteoporosis was higher in the RA patients in comparison with the control. The RA group's frequency of lumbar spine osteoporosis was 32% compared with 5.88% in the healthy volunteers. The femoral neck osteoporosis in the RA group was 16% compared with 9.8% in the control group. Haugeberg et al. agreed with this study's results. They reported in their study that the frequency of osteoporosis in the RA patients was twofold in 4 age groups compared with the reference population, 28.6% in the femoral neck, 29.9% in the total hip, and 31.5% in the spine [6]. Sinigaglia et al. studied RA patients only and observed that osteoporosis in the RA patients was 28.8% at the lumbar spine and 36.2% at the femoral neck [27].

In the current study, age, menopausal years, HAQ-DI, cumulative steroid dose, disease duration, and FRAX of the hip fractures and major osteoporotic fractures had significant relations with BMD of the femoral neck and lumbar spine in the RA group. DAS28-ESR and DAS28-CRP had significant negative correlations with BMD at the femoral neck. Haugeberg et al. agreed with this study. They detected that age, current use of corticosteroids, body weight, and physical disability (measured by HAQ-DI) were significant predictors of BMD at the femoral neck, lumbar spine, and total hip. Also, the RF positivity was a predictor of the femoral neck BMD [6]. In addition, Sinigaglia et al. noted that steroid use, menopause, age, BMI, and HAQ-DI were independent predictors of lumbar and femoral BMD [27].

Lodder et al. also agreed with this study results and reported that older age, high disease activity, and low BMI were related to decreased BMD at the hip and spine. However, they stated that the use of corticosteroids was not independently associated with BMD [28]. This study did not correlate the steroid use with the duration and dosage or cumulative dose.

It was found in this study that the RA patients have a higher fracture risk probability for hip and major fractures significantly compared with the control group. Other studies agreed with these results and demonstrated that RA patients have a higher incidence of osteoporotic fractures than others [29, 32, 33]. Also, the postmenopausal women in the RA group were found in this study to have higher fracture probabilities than those in the control group. Previous studies reported an increased risk of osteoporotic fractures in both genders in the RA patients than the healthy individuals [7]. That suggests that RA is an independent risk factor for fracture. Multiple studies have reported an increased incidence of vertebral and hip fractures in RA patients [7, 32–35].

In this study, it was found that FRAX of hip and major osteoporotic fractures was correlated positively to age, menopausal years, cumulative steroid dose, DAS28-ESR, DAS28-CRP, and HAQ-DI. Also, there were significant negative correlations of the FRAX of hip and major osteoporotic fractures with BMI and BMD of

Table 2 Spearman's correlation of BMD of the femoral head and lumbar spin with other variables in the RA group

	BMD	
	r	***P* value**
Femoral neck		
Age	− 0.426	**< 0.0001**
BMI	0.601	**< 0.0001**
Menopause years	− 0.735	**< 0.0001**
Serum calcium	0.071	0.624
Serum phosphorous	0.185	0.199
HAQ-DI	− 0.442	**0.001**
Cumulative steroid dose	− 0.548	**< 0.0001**
Disease duration	− 0.445	**0.001**
DAS28-ESR	− 0.301	**0.049**
DAS28-CRP	− 0.327	**0.043**
FRAX of major fractures	− 0.741	**< 0.0001**
FRAX of hip fractures	− 0.914	**< 0.0001**
Spine		
Age	− 0.561	**< 0.0001**
BMI	0.652	**< 0.0001**
Menopausal years	− 0.534	**< 0.0001**
Serum calcium	0.05	0.729
Serum phosphorous	0.071	0.622
HAQ-DI	− 0.376	**0.01**
Cumulative steroid dose	− 0.485	**< 0.0001**
Disease duration	− 0.481	**< 0.0001**
DAS28-ESR	− 0.171	0.122
DAS28-CRP	− 0.066	0.235
FRAX of major fractures	− 0.439	**< 0.0001**
FRAX of hip fractures	− 0.612	**< 0.0001**

Statistically significant at P ≤0.05; BMD bone mineral density, *BMI* body mass index, *HAQ-DI* Health Assessment Questionnaire Disability Index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28-ESR* 28 joints disease activity score calculated with ESR, *DAS28-CRP* 28 joints disease activity score calculated with ESR, *FRAX* fracture risk assessment for 10 years fracture probability

Table 3 Spearman's correlation of hip and major fractures FRAX with other variables in the studied subjects in the RA group

	FRAX	
	r	***P* value**
Major fractures		
Age	0.824	**< 0.0001**
BMI	− 0.601	**< 0.0001**
Menopause years	0.529	**< 0.0001**
Serum calcium	− 0.032	0.75
Serum phosphorous	− 0.047	0.637
HAQ-DI	0.623	**< 0.0001**
Cumulative steroid dose	0.368	**0.001**
Current steroid dose	0.115	0.079
DAS28-ESR	0.321	**0.041**
DAS28-CRP	0.355	**0.031**
BMD of total femur (gm/cm^2)	− 0.733	**< 0.0001**
BMD of femoral neck (gm/cm^2)	− 0.836	**< 0.0001**
BMD of lumbar spine (gm/cm^2)	− 0.733	**< 0.0001**
Hip FRAX	0.913	**< 0.0001**
Hip		
Age	0.731	**< 0.0001**
BMI	− 0.652	**< 0.0001**
Menopausal years	0.606	**< 0.0001**
Serum calcium	− 0.06	0.54
Serum phosphorous	− 0.111	0.27
HAQ-DI	0.595	**< 0.0001**
Cumulative steroid dose	0.410	**0.001**
Current steroid dose	0.128	0.086
DAS28-ESR	0.362	**0.037**
DAS28-CRP	0.375	**0.012**
BMD of total femur (gm/cm^2)	− 0.794	**< 0.0001**
BMD of femoral neck (gm/cm^2)	− 0.920	**< 0.0001**
BMD of lumbar spine (gm/cm^2)	− 0.795	**< 0.0001**
Major fractures FRAX	0.913	**< 0.0001**

**Statistically significant at P ≤ 0.05, FRAX* fracture risk assessment for 10 years fracture probability, *BMI* body mass index, *HAQ-DI* Health Assessment Questionnaire Disability Index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28-ESR* 28 joints disease activity score calculated with ESR, *DAS28-CRP* 28 joints disease activity score calculated with CRP, *BMD* bone mineral density

total femur, femoral neck, and lumbar spine. Another study agreed with these results on Chinese RA patients and reported that disease duration, activity, glucocorticoids, BMD of the lumbar spine, and femur neck were significant risk factors of high FRAX of both hip and major osteoporotic fractures [31]. Another study stated that age, BMI, glucocorticoid use, and disease duration were independent risk factors for fracture risk as measured by FRAX in Korean RA patients [30].

Furthermore, it was found in this study that age, BMI, HAQ-DI, DAS28-ESR, and BMD at the femoral neck were significant predictors of FRAX of hip fractures in RA patients using multiple linear regression analysis. Also, age, BMI, menopausal years, HAQ-DI, cumulative steroid dose, and BMD at the femoral head were significant predictors of FRAX of major osteoporotic fractures in RA patients. The interpretation is that BMD of the femoral neck and glucocorticoid use are entries in FRAX online calculator. Low BMD can be related to disease-related factors and other factors affecting BMD. Age, BMI, and menopausal years were established risk factors of low bone mass. Therefore, these factors can increase fractures risk in those patients besides the disease-related factors as disease activity and glucocorticoid use that lower the bone mass. So, bone density and

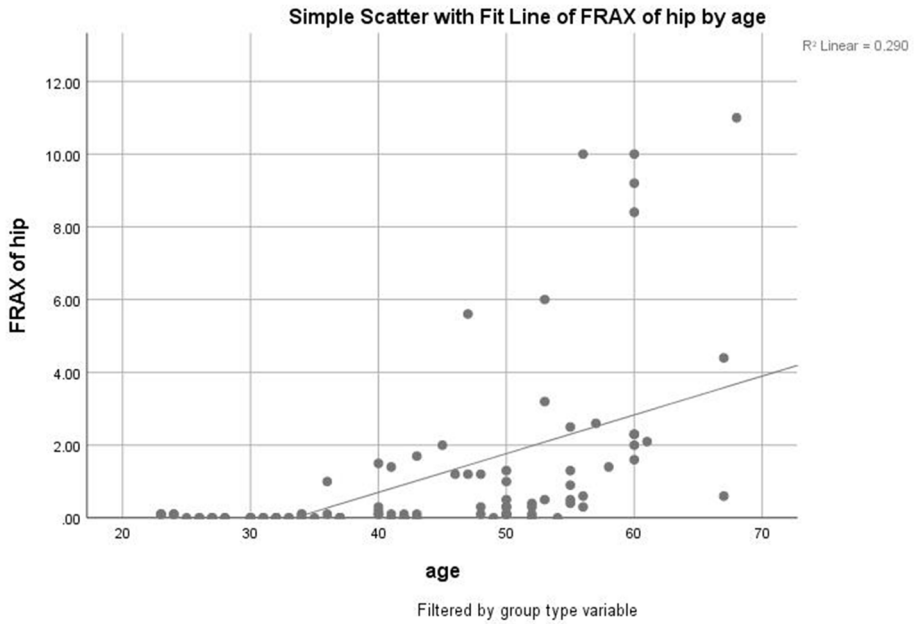

Fig. 2 Significant positive correlation between FRAX of hip fractures and age in RA patients ($P < 0.0001$)

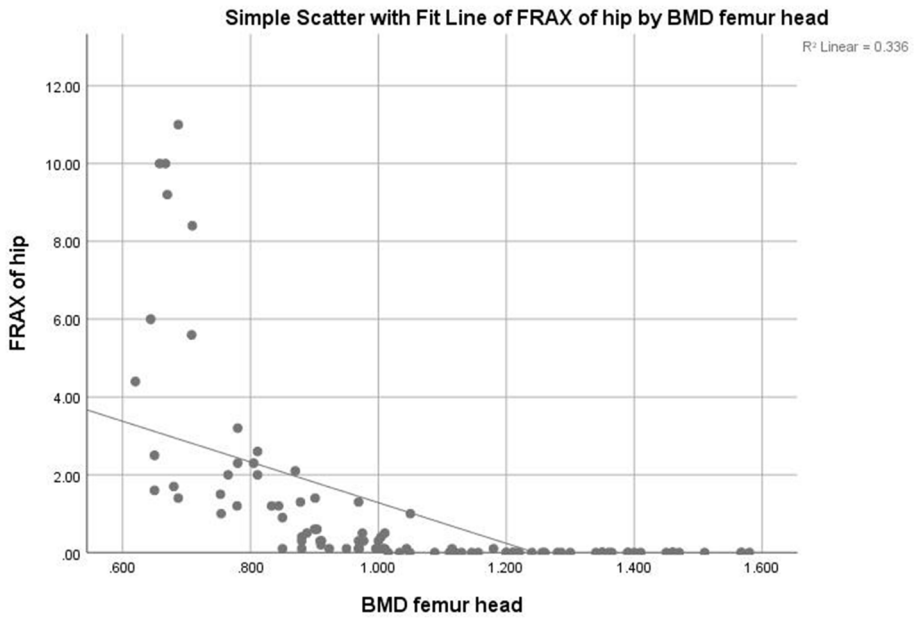

Fig. 3 Significant negative correlation between FRAX of hip fractures and BMD of femoral head in RA patients ($P < 0.0001$)

other affecting factors can be predictors of FRAX of hip and major osteoporotic fractures.

As fracture frequently reduces the best of life, fracture prevention is crucial for patients with RA. First, the fracture hazard must be evaluated in the RA sufferers. Consequently, annual BMD measurement and FRAX calculation should be done to detect osteoporosis and fracture risk in RA patients. Abnormal BMD must be managed carefully with antiresorptive drugs in addition to calcium and vitamin D supplementation to decrease the opportunity of osteoporotic fractures.

Table 4 Multiple linear regression analysis models of the significant predictors of hip and major fractures FRAX in RA patients

	FRAX		
	B	**SE**	***P* value**
Hip			
Constant	− 8.254	5.312	**0.019**
Age	0.225	0.050	**< 0.0001**
Menopausal years	0.294	0.111	0.072
BMI	− 0.246	0.041	**< 0.0001**
Cumulative steroid dose	2.546	0.714	0.112
HAQ-DI	2.822	0.993	**0.013**
DAS28-ESR	1.610	0.656	**0.028**
DAS28-CRP	1.832	0.832	0.050
BMD of femoral neck	− 12.61	1.913	**< 0.0001**
Major fractures			
Constant	− 29.95	4.910	**0.005**
Age	0.381	0.087	**0.001**
Menopausal years	0.518	0.226	**0.001**
BMI	− 0.324	0.08	**0.001**
Cumulative steroid dose	0.301	0.226	**0.030**
HAQ-DI	6.606	1.49	**0.001**
DAS-ESR	3.278	0.888	0.156
DAS-CRP	5.034	1.085	0.09
BMD of femoral neck	− 9.79	4.736	**0.048**

Statistically significant at $P \leq 0.05$, *B* unstandardized beta, *SE* standard error for the unstandardized beta, *FRAX* fracture risk assessment, *BMI* body mass index, *HAQ-DI* Health Assessment Questionnaire Disability Index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28-ESR* 28 joints disease activity score calculated with ESR, *DAS28-CRP* 28 joints disease activity score calculated with CRP, *BMD* bone mineral density

Second, RA disease activity must be controlled. For decades, prednisone can suppress activity, but it could also enhance osteoporosis [36]. On the other hand, methotrexate (MTX) can suppress inflammation and does not affect trabecular bone density [37]. Also, tumor necrosis factor (TNF) inhibitors have indirect anti-resorptive effects on bone through control of inflammation. Currently, the evidence does not suggest that treatment with anti-TNF has any specific beneficial effect on preventing osteoporosis or fractures beyond the control of inflammation compared with conventional nonbiologic regimens [38].

Third, immobility and physical disability are risk factors for bone loss and fracture risk [39], so RA patients should have regular weight-bearing exercises such as walking and running that strengthen the bone and decrease BMD loss. Also, prevention of falls by home safety measures and walking aids may reduce the risk of falling and fracture [40].

There are limitations to the current study. It was performed only in one governorate in Egypt. Also, most of the studied subjects in both groups were females as RA is prevalent in females than males. Matching of both groups regarding gender was done to avoid statistical errors.

This study has several strengths. It studied FRAX in Egyptian RA patients (not studied before). Also, it correlated the results with disease-related factors as disease activity, functional disability, and other factors related to BMD as age, BMI, and menopausal years.

Conclusions

In conclusion, RA patients have a high incidence of abnormal BMD and fracture risk as measured by the FRAX tool than healthy individuals. So regular screening of BMD and FRAX should be done regularly to prevent morbidity of fractures for RA patients.

Abbreviations

RA: Rheumatoid arthritis; BMD: Bone mineral density; FRAX: Fracture Risk Assessment Tool; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; HAQ-DI: Health Assessment Questionnaire Disability Index; BMI: Body mass index; WHO: World Health Organization; DAS28: 28 Joints Disease Activity Score; DAS28-ESR: 28 Joints Disease Activity Score calulated with ESR; DAS28-CRP: 28 Joints Disease Activity Score calculated with CRP; MTX: Methotrexate; TNF: Tumor necrosis factor; DMARD: Disease-modifying antirheumatic drugs; SPSS: Statistical Package for the Social Sciences; DEXA: Dual-energy X-ray absorptiometry; NOF: National Osteoporosis Foundation; US: United States; NOGG: National Osteoporosis Guideline Group; ISCD: International Society for Clinical Densitometry; UK: United Kingdom; RF: Rheumatoid factor; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RANKL: Receptor activator NF-kB ligand; OPG: Osteoprotegerin; Anti-CCP: Anti-cyclic citrullinated peptide antibody.

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Author's contributions

ZN designed the work, collected all data, analyzed data, and drafted the final outcome. The author read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Ethical Committee Board of Faculty of Medicine, Suez Canal University, approved this study. The reference number is 3086/10-5-2019. Written informed consent was taken from all subjects before participating in the study.

Consent for publication

Not applicable.

Competing interests

There are no competing interests for this research.

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References

1. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE (2010) Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955–2007. Arthritis Rheum 62(6):1576-1582. https://doi.org/10.1002/art.27425
2. Aletaha D, Smolen JS (2018) Diagnosis and management of rheumatoid arthritis: a review. Jama 320(13):1360-1372. https://doi.org/10.1001/jama.2018
3. Vis M, Güler-Yüksel M, Lems W (2013) Can bone loss in rheumatoid arthritis be prevented? Osteoporos Int 24(10):2541-2553. https://doi.org/10.1007/s00198-013-2334-5
4. Miao C-g, Yang Y-y, He X, Li X-f, Huang C, Huang Y, Zhang L, Lv X-W, Jin Y, Li J (2013) Wnt signaling pathway in rheumatoid arthritis, with special emphasis on the different roles in synovial inflammation and bone remodeling. J Cell Signal 25(10):2069-2078. https://doi.org/10.1016/j.cellsig.2013.04.002
5. Kleyer A, Finzel S, Rech J, Manger B, Krieter M, Faustini F, Araujo E, Hueber AJ, Harre U, Engelke KJA (2014) Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies. Ann Rheum Dis 73(5):854-860. https://doi.org/10.1136/annrheumdis-2012-202958
6. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK (2000) Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. Arthritis Rheum 43(3):522-530. https://doi.org/10.1002/1529-0131(200003)43:3<522::AID-ANR7>3.0.CO;2-Y
7. Xue A-L, Wu S-Y, Jiang L, Feng A-M, Guo H-F, Zhao P (2017) Bone fracture risk in patients with rheumatoid arthritis: a meta-analysis. Medicine 96(36). https://doi.org/10.1097/MD.0000000000006983
8. Jin S, Hsieh E, Peng L, Yu C, Wang Y, Wu C, Wang Q, Li M, Zeng X (2018) Incidence of fractures among patients with rheumatoid arthritis: a systematic review and meta-analysis. Osteoporos Int 29(6):1263-1275. https://doi.org/10.1007/s00198-018-4473-1
9. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian J, Binkley N, Cauley JA, Compston JE, Dawson-Hughes B, Fuleihan GE-HJO (2011) Interpretation and use of FRAX in clinical practice. Osteoporos Int 22(9):2395-2411. https://doi.org/10.1007/s00198-007-0543-5
10. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MDJA (2010) 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 62(9):2569-2581. https://doi.org/10.1002/art.27584
11. Joshi A, Varthakavi P, Chadha M, Bhagwat NJJ (2013) A study of bone mineral density and its determinants in type 1 diabetes mellitus. J Osteoporos 2013. https://doi.org/10.1155/2013/397814
12. Deshmukh H, Papageorgiou M, Aye M, England J, Abdalla M, Sathyapalan TJCE (2021) Hyperthyroidism and bone mineral density: dissecting the causal association with Mendelian randomization analysis. Clin Endocrinol 94(1):119-127. https://doi.org/10.1155/2013/397814
13. Stensland SH, Margolis SJJADA (1990) Simplifying the calculation of body mass index for quick reference. J Am Diet Assoc 90(6):856
14. Gale S, Wilson JC, Chia J, Trinh H, Tuckwell K, Collinson N, Dimonaco S, Jick S, Meier C, Mohan SVJR (2018) Risk associated with cumulative oral glucocorticoid use in patients with giant cell arteritis in real-world databases from the USA and UK. Rheumatol Ther 5(2):327-340. https://doi.org/10.1007/s40744-018-0112-8
15. Bruce B, Fries JF (2003) The Stanford health assessment questionnaire: dimensions and practical applications. Health Qual Life Outcomes 1(1):1-6. https://doi.org/10.1186/1477-7525-1-20
16. Prevoo M, Van'T Hof MA, Kuper H, Van Leeuwen M, Van De Putte L, Van Riel P (1995) Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 38(1):44-48. https://doi.org/10.1002/art.1780380107
17. Jeremiah MP, Unwin BK, Greenawald MH, Casiano VE (2015) Diagnosis and management of osteoporosis. Am Fam Physician 92(4):261-268
18. Bhalla AK (2010) Management of osteoporosis in a pre-menopausal woman. Best Prac Res Clin Rheumatol 24(3):313-327. https://doi.org/10.1016/j.berh.2010.01.006
19. Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi M-L, Kalkwarf HJ, Langman CB, Plotkin H, Rauch FJB (2008) International Society for Clinical Densitometry 2007 adult and pediatric official positions. Bone 43(6):1115-1121. https://doi.org/10.1002/jbmr.5650090802
20. Fowler EG, Rao S, Nattiv A, Heberer K, Oppenheim WL (2015) Bone density in premenopausal women and men under 50 years of age with cerebral palsy. J Phys Med Rehabil 96(7):1304-1309. https://doi.org/10.1016/j.apmr.2015.03.012
21. Kanis JA, Johansson H, Harvey NC, McCloskey EV(2018) A brief history of FRAX. Arch Osteoporos13(1):1-16. https://doi.org/10.1007/s11657-018-0510-0
22. Dawson-Hughes B, Tosteson A, Melton L, Baim S, Favus M, Khosla S, Lindsay RJ (2008) Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. Osteoporos Int 19(4):449-458. https://doi.org/10.1007/s00198-008-0559-5
23. Cauley JA, Fuleihan GE-H, Arabi A, Fujiwara S, Ragi-Eis S, Calderon A, Chionh SB, Chen Z, Curtis JR, Danielson ME (2011) Official positions for FRAX® clinical regarding international differences: from joint official positions development conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®. J Clin Densitom 14(3):240-262. https://doi.org/10.1016/j.jocd.2011.05.015
24. Wright NC, Walitt BT, Eaton CB, Chen Z (2011) Arthritis increases the risk for fractures—results from the Women's Health Initiative. J Rheumatol 38(8):1680-1688. https://doi.org/10.3899/jrheum.101196
25. Kim D, Cho S-K, Choi C-B, Jun J-B, Kim T-H, Lee H-S, Lee J, Lee S-S, Yoo D-H, Yoo W-H (2016) Incidence and risk factors of fractures in patients with rheumatoid arthritis: an Asian prospective cohort study. Rheumatol Int 36(9):1205-1214. https://doi.org/10.1007/s00296-016-3453-z
26. Wang Y, Hao Y, Deng X, Li G, Geng Y, Zhao J, Zhou W, Zhang Z (2015) Risk factors for bone mineral density changes in patients with rheumatoid arthritis and fracture risk assessment. Beijing da xue xue bao Yi xue ban= Journal of Peking University. Health Sciences 47(5):781-786
27. Sinigaglia L, Nervetti A, Mela Q, Bianchi G, Del Puente A, Di Munno O, Frediani B, Cantatore F, Pellerito R, Bartolone S (2000) A multicenter cross-sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. J Rheumatol 27(11):2582-2589
28. Lodder M, de Jong Z, Kostense P, Molenaar E, Staal K, Voskuyl A, Hazes J, Dijkmans B, Lems W (2004) Bone mineral density in patients with rheumatoid arthritis: relation between disease severity and low bone mineral density. Ann Rheum Dis 63(12):1576-1580. https://doi.org/10.1136/ard.2003.016253
29. Tong J-j, Xu S-q, Zong H-x, Pan M-j, Teng Y-z, Xu J-hC (2020) Prevalence and risk factors associated with vertebral osteoporotic fractures in patients with rheumatoid arthritis. Clin Rheumatol 39(2):357-364. https://doi.org/10.1007/s10067-019-04787-9
30. Choi ST, Kwon S-R, Jung J-Y, Kim H-A, Kim S-S, Kim SH, Kim J-M, Park J-H, Suh C-HJJ (2018) Prevalence and fracture risk of osteoporosis in patients with rheumatoid arthritis: a multicenter comparative study of the FRAX and WHO Criteria. J Clin Med 7(12):507. https://doi.org/10.3390/jcm7120507
31. Meng J, Li Y, Yuan X, Lu Y (2017) Evaluating osteoporotic fracture risk with the Fracture Risk Assessment Tool in Chinese patients with rheumatoid arthritis. Medicine 96. https://doi.org/10.1097/MD.0000000000006677
32. Kim SY, Schneeweiss S, Liu J, Daniel GW, Chang C-L, Garneau K, Solomon DH (2010) Risk of osteoporotic fracture in a large population-based cohort of patients with rheumatoid arthritis. Arthritis Res Ther 12(4):1-10. https://doi.org/10.1186/ar3107
33. Brennan SL, Toomey L, Kotowicz MA, Henry MJ, Griffiths H, Pasco JA (2014) Rheumatoid arthritis and incident fracture in women: a case-control study. BMC Musculoskelet Disord 15(1):1-6. https://doi.org/10.1186/1471-2474-15-13
34. Mazzucchelli R, Fernandez EP, Crespí-Villarías N, Quirós-Donate J, Vadillo AG, Espinosa M, Peña M, Macía-Villa C, Morell-Hita JL, Martinez-Prada CJR (2018) 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(1):e000671. https://doi.org/10.1136/rmdopen-2018-000671
35. Mohammad A, Lohan D, Bergin D, Mooney S, Newell J, O'Donnell M, Coughlan RJ, Carey JJ (2014) The prevalence of vertebral fracture on vertebral fracture assessment imaging in a large cohort of patients with rheumatoid arthritis. Rheumatology (Oxford) 53(5):821-827. https://doi.org/10.1093/rheumatology/ket353

36. Compston J (2018) Glucocorticoid-induced osteoporosis: an update. Endocrine 61(1):7-16. https://doi.org/10.1007/s12020-018-1588-2
37. Mazzantini M, Di Munno O, Incerti-Veechi L, Pasero G (2000) Vertebral bone mineral density changes in female rheumatoid arthritis patients treated with low-dose methotrexate. Clin Exp Rheumatol 18(3):327-332
38. Kawai VK, Stein CM, Perrien DS, Griffin MR (2012) Effects of anti-tumor necrosis factor α (anti-TNF) agents on bone. Curr Opin Rheumatol 24(5):576. https://doi.org/10.1097/BOR.0b013e328356d212
39. de Brito CMM, Battistella LR, Guarita MLC (2018) Challenges and complications of immobility. In: Topics in Cognitive Rehabilitation in the TBI Post-Hospital Phase. Springer, p 25-33. https://doi.org/10.1007/978-3-319-95376-2_4
40. Santesso N, Carrasco-Labra A, Brignardello-Petersen R (2014) Hip protectors for preventing hip fractures in older people. Cochrane Database of Systematic Reviews (3). https://doi.org/10.1002/14651858.CD001255.pub5. John Wiley & Sons, Ltd

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