



Clinical science

Bone mineral density and fractures in patients with rheumatoid arthritis: the DXA-HIP project

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Abstract

Objectives: RA is a chronic disabling disease affecting 0.5–1% of adults worldwide. People with RA have a greater prevalence of multimorbidity, particularly osteoporosis and associated fractures. Recent studies suggest that fracture risk is related to both non-RA and RA factors, whose importance is heterogeneous across studies. This study seeks to compare baseline demographic and DXA data across three cohorts: healthy controls, RA patients and a non-RA cohort with major risk factors and/or prior major osteoporotic fracture (MOF).

Methods: This is a cross-sectional study using data collected from three DXA centres in the west of Ireland from January 2000 to November 2018.

Results: Data were available for 30 503 subjects who met our inclusion criteria: 9539 (31.3%) healthy controls, 1797 (5.9%) with RA and 19167 (62.8%) others. Although age, BMI and BMD were similar between healthy controls, the RA cohort and the other cohort, 289 (16.1%) RA patients and 5419 (28.3%) of the non-RA cohort had prior MOF. In the RA and non-RA cohorts, patients with previous MOF were significantly older and had significantly lower BMD at the femoral neck, total hip and spine.

Conclusion: Although age, BMI and BMD were similar between a healthy control cohort and RA patients and others with major fracture risk factors, those with a previous MOF were older and had significantly lower BMD at all three measured skeletal sites. Further studies are needed to address the importance of these and other factors for identifying those RA patients most likely to experience fractures.

Lay Summary

What does this mean for patients?

Rheumatoid arthritis (RA) is a disabling disease affecting millions of people worldwide. This disease causes pain, disability and other problems. RA affects not only joints (e.g. hip, knee, wrist), but also the bones, lungs, eyes and other body tissues. International studies show that people with RA are almost three times as likely to break a bone as the general population. Experts conclude that this is because of bone loss from the inflammation in RA. We measure bone mineral density (BMD) to manage osteoporosis in clinical practice with a test known as a DXA scan. People with lower BMD are more likely to break bones, causing further suffering and illness. In this study, we found that Irish patients with RA are much more likely to have fractures. An especially interesting finding in our study is that although the RA patients had similar age and BMD to healthy controls, far more of them had fractures. However, those with broken bones had lower BMD than those without, whether they had RA or not. Our findings suggest that more research is needed to gain a better understanding of why RA patients are prone to fractures, in order to prevent fracture occurrence in future.

Keywords: rheumatoid arthritis, fracture, DXA, BMD, risk factor.

Key messages

- One in six Irish RA patients have major osteoporotic fractures.
- RA patients have similar BMD to healthy controls without fractures.
- Other fracture risk factors were common among RA patients and others with fractures.

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Introduction

RA is a chronic systemic inflammatory disease affecting 0.5–1% of the adult population of the world [1, 2]. When left untreated, RA is a debilitating disease that affects many body tissues, in particular, synovial joints and the skeleton [1–4]. Multimorbidity and co-morbidities are well-recognized features of this illness, which include a greater incidence of osteoporotic fractures and other skeletal disorders [4–10]. Their presence in RA populations is associated with a greater illness burden, more resistant disease and a higher mortality [5–7, 10].

Low BMD, particularly as measured by central DXA, is the most important predictor of fragility fractures in men and women without prior fracture [11, 12]. Estimation of fracture risk can be greatly improved by combining BMD with other risk factors, in particular age, CSs and other clinical risk factors [12–14]. The presence of RA confers a greater overall risk even after adjustment for such factors [13, 15–18]. This greater propensity to fracture among people with RA is related to traditional fracture risk factors and RA-specific factors, including disease duration, severity and activity, co-morbidities and, certainly, the use of CSs [3, 6, 7, 15, 16, 18–20].

Bone loss occurs early in RA [3, 20], and younger RA patients also have a greater propensity to fracture [21, 22]. Current algorithms underestimate the risk of fracture in some populations at particular risk; they perform poorly in younger adults [12, 23]. Although RA is the only disease specifically included in one of the most widely cited algorithms, its inclusion is limited to a binary yes or no answer [14]. These limitations and the widespread recognition of the importance of both RA and non-RA risk factors suggest that consideration to develop an algorithm specific for RA populations is warranted. In this paper, we present a comparison between our RA cohort, a healthy control cohort and a third cohort, either sharing important risk factors or with prevalent osteoporotic fractures at the time of their first DXA scan.

Methods

Study cohort

Data were retrieved from three hospital sites incorporating four DXA machines, which were used to collect DXA scan data, as previously described [24, 25]. The original cohort consisted of 36 590 subjects with medical histories, medications and a variety of DXA characteristics. In this study, we include Caucasian subjects aged ≥40 years with a valid DXA scan of either the proximal femur or lumbar spine or both. The sample of 33 344 patients, which includes 28 933 women, is presented in Fig. 1. Approval for the collection and analysis of data and a waiver of consent for this study were approved by our local Clinical Research Ethics Committees, Galway University Hospitals: C.A. 2109 and Sligo University Hospitals: 660, and an extension has been granted in 2023 for another year. We divided the sample into three distinct cohorts for further study: a healthy control cohort without prior major osteoporotic fracture (MOF) or major risk factor (MRF) for fracture other than age or being postmenopausal (Healthy cohort); an RA cohort who had been diagnosed with RA by their consultant rheumatologist (see authors) (RA cohort) and another cohort who had prior MOF and/or the presence of additional important MRFs for fracture, such as CSs, a family history of osteoporosis or smoking (Other cohort).

Variables included

Subject demographics included age, height, weight and BMI. We included all available major osteoporotic fracture risk factors as outlined in the FRAX tool, which includes RA [14], and others deemed clinically important by the consultant expert physicians, such as falls, frailty and hormonal therapy for breast, prostate and other cancers [24, 25]. A family history of osteoporosis was not specifically defined as a father or mother with a hip fracture in this data set. DXA biometrics include BMD (in grams per centimetre squared), T-scores calculated using white female NHANES III reference populations for the total femur and femoral neck, and GE Lunar white female for the lumbar spine. These were obtained by International Society for Clinical Densitometry (ISCD) trained and certified professionals as previously described [24, 25]. RA features and treatments, DXA images and other biometrics are not included in this paper.

Fractures

As suggested by [14, 26], fractures were classified into one of three groups: MOFs include fractures as defined by the European Medicines Agency (vertebrae, femur, forearm, humerus, rib, pelvis and tibia); not a MOF (nMOF), whose site is known (e.g. fingers, toes); and other fractures (other), where a prior fracture was reported but could not be validated or when the site was unknown.

We chose to perform our initial analysis on only those whose fractures that were validated and included in the first two groups. Additional analyses were performed including those in the third group as a form of sensitivity analysis to challenge the robustness of our findings.

Analyses

Variables are both binary and continuous and are summarized as proportions or means, as appropriate. We used ANOVA to compare between groups for continuous variables, and a χ^2 test was performed for categorical variables. A *P*-value of <0.05 was deemed statistically significant. All analyses were performed in IBM SPSS Statistics, v.26. and R Studio version 4.2.1. The collection and analysis of the data used in this study was supported, in part, by a grant from the Health Research Board of Ireland: S.D.A.P._2021_001.

Results

After data merging and cleaning, data were available for 33 344 subjects aged ≥40 years with a valid DXA scan of either the proximal femur or lumbar spine or both (see Fig. 1). We excluded 2841 patients who reported having a prior fracture whose site was unknown or could not be validated. Characteristics of the remaining 30 503 subjects are presented in Table 1 and broken down by sex in Table 2. The patients in the RA cohort were older and had higher BMI and a greater proportion of men than either the Healthy or Other cohorts, whilst the mean age and BMI of the Healthy and Other cohorts were similar.

As expected, the prevalence of other MRFs was substantial in the RA and Other cohorts. Smoking, alcohol and osteoporosis medication use were similar between the RA and Other cohort, whereas the use of glucocorticoids and the presence of other risk factors was greater among the RA cohort. The presence of a family history of osteoporosis was more than three

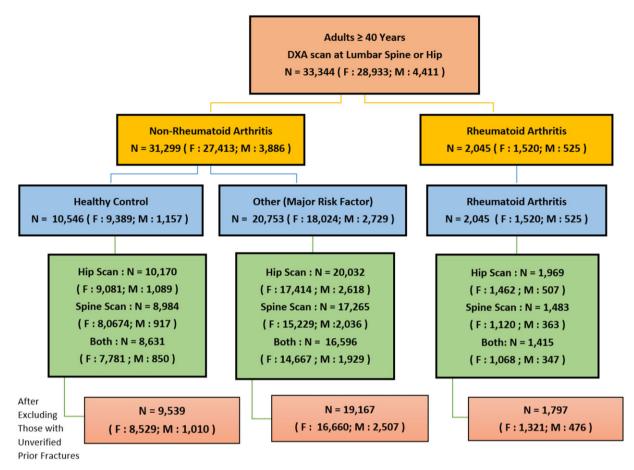


Figure 1. Derivation of the cohorts

Table 1. Characteristics of the three cohorts

Characteristic	Healthy	RA	Other	
n (%)	9539 (31.3)	1797 (5.9)	19 167 (62.8)	
Female, <i>n</i> (%)	8529 (89.4)	1321 (73.5)	16 660 (86.9)	
Age, mean (s.D.), years	62.70 (11.20)	64.07 (10.63)	62.83 (11.23)	
BMI, mean (s.D.), kg/m ²	26.66 (4.88)	27.48 (5.24)	26.74 (5.15)	
Family history, n (%)	0	120 (6.7)	4085 (21.3)	
Glucocorticoid use, n (%)	0	556 (30.9)	2862 (14.9)	
Smoker, <i>n</i> (%)	0	203 (11.3)	2568 (13.4)	
Excess alcohol use, n (%)	0	17 (0.9)	137 (0.7)	
Major osteoporotic fracture, n (%)	0	289 (16.1)	5419 (28.3)	
Other fracture, n (%)	252 (2.6)	43 (2.4)	405 (2.1)	
Total fractures, <i>n</i> (%)	252 (2.6)	332 (18.5)	5824 (30.4)	
Other risk factors, n (%)	0	1797 (100)	15 044 (78.5)	
Femoral neck BMD, mean (s.D.), g/cm ²	0.868 (0.150)	0.873 (0.162)	0.850 (0.146)	
Total hip BMD, mean (s.D.), g/cm ²	0.918 (0.160)	0.922 (0.175)	0.899 (0.163)	
Lumbar spine BMD, mean (s.D.), g/cm ²	1.070 (0.193)	1.096 (0.201)	1.048 (0.192)	
Taking osteoporosis medication (%)	1806 (18.9)	656 (36.5)	6771 (35.3)	
T-score ≤ -2.5 , n (%)	1615 (16.9)	229 (12.7)	3707 (19.3)	

times greater in the Other cohort compared with the RA cohort, with no incidence in the Healthy cohort.

BMD

Men had higher BMD at the lumbar spine, femoral neck and total hip than women in all three cohorts, as shown in Fig. 2 and Table 2. Although there were some differences in BMD

between the three cohorts, more noticeably when broken down by sex (as shown in Table 2 and Fig. 2), these differences were small (i.e. of the order of less than one-third of a standard deviation). Although the Healthy cohort were younger and had no known MRF or prior MOF, they had similar BMD at the proximal femur to the RA cohort, whereas those in the Other cohort had lower hip and spine BMD.

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Table 2. Characteristics of the female and male cohorts

Characteristic	Healthy	RA	Other	P-value
Female				
n (%)	8529 (32.2)	1321 (5)	16 660 (62.8)	
Age, mean (s.D.), years	62.32 (10.95)	63.47 (10.53)	62.29 (11.09)	0.001
Height, mean (s.D.), cm	160.66 (6.33)	159.39 (6.27)	160.16 (6.58)	0.000
Weight, mean (s.D.), kg	68.58 (13.13)	69.62 (14.84)	68.40 (13.96)	0.007
BMI, mean (s.D.), kg/m ²	26.57 (4.90)	27.38 (5.51)	26.66 (5.21)	0.000
Smokers, n (%)	0	151 (11.4)	2241 (13.5)	0.000
Excess alcohol, n (%)	0	6 (0.5)	73 (0.4)	0.000
Glucocorticoid use, n (%)	0	372 (28.2)	2040 (12.2)	0.000
Postmenopausal, n (%)	4639 (54.4)	1116 (84.5)	11 607 (69.7)	0.000
Family history of osteoporosis, <i>n</i> (%)	0	99 (7.5)	3882 (23.3)	0.000
Other risk factors, n (%)	0	1321 (100)	13 178 (79.1)	0.000
Major osteoporotic fracture, n (%)	0	239 (18.1)	4757(28.5)	0.000
Other fracture, <i>n</i> (%)	222 (2.6)	36 (2.7)	354 (2.1)	0.000
Total fractures, <i>n</i> (%)	222 (2.6)	275 (20.8)	5111 (30.7)	0.000
Mean femoral neck BMD, mean (s.D.), g/cm ²	0.863 (0.147)	0.849 (0.148)	0.843 (0.144)	0.000
Mean total hip BMD, mean (s.D.), g/cm ²	0.910 (0.156)	0.891 (0.163)	0.890 (0.160)	0.000
Mean lumbar spine BMD, mean (s.D.), g/cm ²	1.061 (0.186)	1.060 (0.190)	1.033 (0.184)	0.000
T-score $\leq -2.5, n$ (%)	1522 (17.8)	209 (15.8)	3425 (20.5)	0.000
Taking osteoporosis medication, n (%)	1722 (20.2)	541 (40.9)	6217 (37.3)	0.000
Male	,	,	,	
n (%)	1010 (25.3)	476 (11.9)	2507 (62.8)	
Age, mean (s.D.), years	65.92 (12.67)	65.74 (10.53)	66.40 (11.48)	0.355
Height, mean (s.D.), cm	172.24 (7.51)	172.17 (6.97)	172.15 (7.15)	0.945
Weight, mean (s.D.), kg	81.43 (15.47)	82.50 (14.91)	81.03 (15.49)	0.156
BMI, mean (s.D.), kg/m ²	27.40 (4.63)	27.77 (4.40)	27.28 (4.67)	0.109
Smokers, n (%)	0	52 (10.9)	327 (13)	0.000
Excess alcohol, n (%)	0	11 (2.3)	64 (2.6)	0.000
Glucocorticoid use, <i>n</i> (%)	0	184 (38.7)	822 (32.8)	0.000
Family history of osteoporosis (%)	0	21 (4.4)	203 (8.1)	0.000
Other risk factors, n (%)	0	476 (100)	1866 (74.4)	0.000
Major osteoporotic fracture, n (%)	0	50 (10.5)	662 (26.4)	0.000
Other fracture, n (%)	30 (3)	7 (1.5)	51 (2)	0.000
Total fractures, <i>n</i> (%)	30 (3)	57 (12)	713 (28.4)	0.000
Mean femoral neck BMD, mean (s.D.), g/cm ²	0.913 (0.169)	0.940 (0.180)	0.890 (0.159)	0.000
Mean total hip BMD, mean (s.D.), g/cm ²	0.989 (0.176)	1.013 (0.177)	0.959 (0.173)	0.000
Mean lumbar spine BMD, mean (s.D.), g/cm ²	1.171 (0.227)	1.201 (0.197)	1.140 (0.221)	0.000
T-score ≤ -2.5 , n (%)	93 (9.2)	20 (4.2)	228 (9.1)	0.000
Taking osteoporosis medication, n (%)	84 (8.3)	115 (24.2)	554 (22.1)	0.000

In contrast, when these were broken down by sex, women in the Healthy cohort had slightly higher BMD than those in the RA and Other cohorts, although the Healthy and Other cohorts were similar in age and BMI, whereas the RA cohort were slightly older and had a higher BMI. Notwithstanding that the men in the RA cohort were similar in age to the Healthy cohort, they had a slightly higher BMI and higher BMD at proximal femur and lumbar spine. The Other cohort were older and had slightly lower BMI and BMD at all three sites compared with both the Healthy and RA cohorts. The proportion of men and women whose lowest BMD was in the osteoporotic range was lowest among the RA cohort.

Fractures

After exclusion of 2841 subjects whose fracture site and veracity could not be established, 6408 subjects remained with 7043 prior fractures: 5708 MOF, 1035 nMOF, and 335 with MOF and nMOF. The prevalence of nMOF fractures (ankle, calcaneum, coccyx, fibula, mandible, metacarpals, metatarsals, navicular, toe, thumb, finger, nose, mandible, talus, scaphoid, carpals, cuboid, face, foot, hand, patella, phalanges, phalanx) was similar across all three cohorts for both sexes. Although the Healthy cohort were not too dissimilar in terms

of age, BMI and BMD, clearly the prevalence of MOF in the RA and Other cohorts differed, probably reflective of the presence of other major risk factors, such as glucocorticoids, and referral bias.

The proportion of men and women with an MOF was greater among the Other cohort than the RA cohort despite a lower prevalence of glucocorticoid use and other MRF (Table 2). Table 3 details the site and number of MOF in each group aggregated by sex. The wrist and forearm were the most common site of fracture, followed by other MOF (ribs, tibia, pelvis, clavicle and scapula). A similar proportion of fractures occurred at the spine and hip in both the RA and Other cohorts among women, whereas very few men with RA suffered a prior humeral fracture. Despite considerable overlap, patients with prevalent MOF had significantly lower BMD compared with those without, in both the RA and Other cohorts (Fig. 2). Those patients with prior MOF were significantly older and had significantly lower BMD at the femoral neck, total hip and lumbar spine in both the RA and Other cohorts. Analyses that included those with a possible prior fracture that could not be verified showed similar results for age, BMI and BMD within and between cohorts (results not shown).

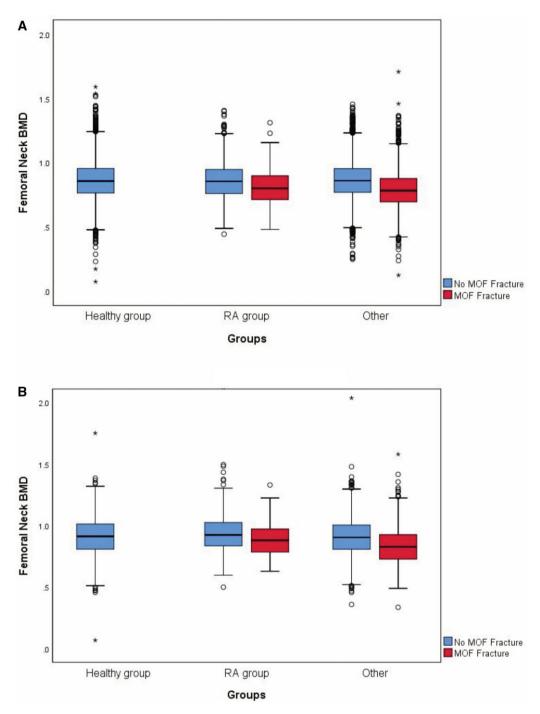


Figure 2. Femoral neck BMD in subjects with and without major osteoporotic fractures. (A) female subjects. (B) male subjects

Discussion

In this paper, we present preliminary data examining some of the features of our cohort with RA compared with a cohort of healthy controls and another sharing similar risk factors. Although age, BMI and BMD was similar across the three cohorts, 1 in 10 men and almost 1 in 5 women with RA had a prior MOF, while more than 1 in 4 men and women in the other cohorts had a prior MOF. The prevalence of MRF is clearly very different in the RA and Other cohorts, which is likely to account for much of these differences. These data serve as a data-

rich repository to explore the risk factors for, and associations with, MOF in patients with RA compared with healthy controls and others with similar MRF in our population. It is clearly established that RA patients have a greater risk of MOF than non-RA populations [3, 7, 16, 17, 21, 22, 27, 28], which represents one of the most common co-morbidities for these patients [5–7, 16, 18, 19, 21, 22]. This concept, and the results of a meta-analysis of multiple cohorts, led to the inclusion of RA as a distinct factor when estimating the presence of osteoporosis or future fracture risk [12]. A number of reasons for this greater

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risk have been stipulated, including traditional fracture risk factors and RA-specific factors [18].

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BMD is considered the single best predictor of fracture in men and women without prior fracture, and the best way to make a clinical diagnosis of osteoporosis in the absence of an MOF [12]. Bone loss occurs early in RA and is associated with greater disease activity and use of glucocorticoids [3, 7, 18, 20]. However, two of the largest studies, which included >40 000 RA patients, did not include BMD in their analyses [7, 17]. US data from the NHANES III cohort shows that RA patients have similar proximal femur BMD to those without [15]. A recent meta-analysis of fracture incidence in RA reported only two studies showing an association with low BMD [18]. Others have suggested that RA predicts fracture independent of BMD, CS use and other risk factors, although limited data on the accuracy of the diagnosis are available, and no other RA-specific data are included [13].

A recent meta-analysis summarized other features associated with fracture risk in RA populations [18]. These include non-RA features, such as older age, low BMI, use of glucocorticoids, comorbidities and disability. RA features include disease duration,

Table 3. Number of fractures by site amongst the female and male cohorts

Fractures	Healthy	RA	Other	
Female				
Vertebra, n (%)	0	41 (11.7)	641 (10.3)	
Hip, n (%)	0	31 (8.8)	593 (9.5)	
Wrist and forearm, n (%)	0	109 (31.1)	2805 (45.1)	
Humerus, n (%)	0	47 (13.4)	510 (8.2)	
Other MOF, n (%)	0	73 (20.8)	1025 (16.5)	
Other fractures	222 (100)	50 (14.2)	640 (10.3)	
(not MOF), <i>n</i> (%)				
Total fractures, <i>n</i> (%)	222	351	6214	
Male				
Vertebra, n (%)	0	10 (14.7)	185 (21.6)	
Hip, <i>n</i> (%)	0	9 (13.2)	151 (17.6)	
Wrist and forearm, n (%)	0	19 (27.9)	182 (21.2)	
Humerus, n (%)	0	1 (1.5)	74 (8.6)	
Other MOF, n (%)	0	18 (26.5)	184 (21.4)	
Other fractures	30 (100)	11 (16.2)	82 (9.5)	
(not MOF), <i>n</i> (%)				
Total fractures, <i>n</i> (%)	30	68	858	

MOF: major osteoporotic fracture.

extra-articular manifestations, major joint surgery and disease activity. Only older age and CS use were consistently noted [18]. In our study, we found that those with prior MOF had significantly lower BMD at all three skeletal sites compared with those without. The prevalence of other risk factors, such as smoking, glucocorticoid use and family history, was similar or even higher among those without MOF compared with those with prior MOF, as shown in Table 4.

Many of the most widely used osteoporosis identification and fracture risk prediction tools today include RA, some as the sole additional disease, although none include RA-specific features [12]. Not all studies have compared RA with healthy controls and with those with other MOF and RF [7, 13, 15, 17, 18, 22]. Our study is uniquely placed to help determine which RA-specific features are important to consider in addition to general fracture risk factors among our RA populations to improve risk assessment. This might be particularly helpful for younger patients with RA, for whom fractures are a problem [21, 22], and for whom current risk assessment tools underperform [29]. Although we have previously shown that vertebral fractures among our RA population are associated with disease activity and duration [30], we have not included RA-specific features in this paper, which are being examined in a longitudinal analysis assessing fracture risk. Our study has other important limitations, including a significant referral bias, in that all included patients had a DXA scan. We have a small sample size for some MOF skeletal sites, particularly among men. This study is cross-sectional in nature, but these data represent preliminary analyses, and future studies will address future risk. We do not have a complete validated set of data on every patient, because some episodes of care happen at other facilities outside our system, hence the possibility of missing data is real and probable, which might affect results. We excluded those with prior fractures that could not be validated, and although reports and images are assessed, it is possible that some fractures were missed among those included. Although the proportion of those with RA and in the Other cohort taking osteoporosis medication was similar, and a proportion of both are taking glucocorticoids, we have limited data on medication dose, duration, adherence and compliance, which could also influence our results. Accessing comprehensive and accurate clinical data from real-world cohorts is problematic, whereas

Table 4. Characteristics of RA and Other cohorts by major osteoporotic fracture status

Characteristic	RA			Other		
	MOF	No MOF	P-value	MOF	No MOF	P-value
n (%)	289 (16.1)	1508 (83.9)	_	5419 (28.3)	13 748 (71.7)	_
Female (%)	239 (82.7)	1082 (71.8)	_	4757 (87.8)	11 903 (86.6)	_
Age, mean (s.D.), years	66.02 (10.85)	63.69 (10.55)	0.001	66.30 (11.45)	61.45 (10.84)	0.000
BMI, mean (s.D.), kg/m ²	27.42 (5.35)	27.49 (5.22)	0.832	26.49 (5.13)	26.84 (5.16)	0.000
Smokers, n (%)	24 (8.3)	179 (11.9)	0.079	539 (9.9)	2029 (14.8)	0.000
Alcohol abuse, n (%)	3 (1)	14 (0.9)	0.860	50 (0.9)	87 (0.6)	0.032
Glucocorticoid use, n (%)	88 (30.4)	468 (31)	0.844	477 (8.8)	2385 (17.3)	0.000
Postmenopausal, n (%)	220 (92)	896 (82.8)	0.000	3676 (77.3)	7931 (66.6)	0.000
Family history of osteoporosis, n (%)	14 (4.8)	106 (7)	0.173	769 (14.2)	3316 (24.1)	0.000
Femoral neck BMD, mean (s.D.), g/cm ²	0.822 (0.143)	0.883 (0.164)	0.000	0.796 (0.143)	0.870 (0.143)	0.000
Total hip BMD, mean (s.D.), g/cm ²	0.861 (0.163)	0.934 (0.175)	0.000	0.838 (0.162)	0.922 (0.160))	0.000
Lumbar spine BMD, mean (s.D.), g/cm ²	1.023 (0.204)	1.113 (0.197)	0.000	0.993 (0.189)	1.068 (0.188)	0.000
T-score $\leq -2.5, n$ (%)	58 (20.1)	171 (11.3)	0.000	1504 (27.8)	2203 (16)	0.000
Taking osteoporosis medication, n (%)	173 (59.9)	483 (32)	0.000	2371 (43.8)	4400 (32)	0.000

MOF: major osteoporotic fracture.

biometric data, such as height, weight and BMD, are more readily available. Additional DXA data could thus help to identify those most likely to fracture and are currently being submitted in an additional publication. Finally, these data represent patients from three different centres in the west of Ireland, which might not be reflective of other regions.

Conclusion

In this paper, we present preliminary data on a cohort of RA patients compared with a healthy control group and another reference group referred for DXA scans to assess their risk of fracture and presence of low BMD or osteoporosis. Almost one in five RA patients and more than one in four of an at-risk group had prevalent MOF. Although baseline age, BMI and BMD were similar across these three cohorts, those with prior MOF had significantly lower BMD at each measured site. These data suggest that BMD is important to help identify those at risk, and other DXA biometrics and RA features warrant further exploration in future studies. Referral bias, missing data and the cross-sectional nature of our study are important limitations.

Data availability

These data are not publicly available; a limited anonymized data set could be made available by contacting the corresponding author and with the appropriate permissions.

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