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Original article

Predictors of fragility fracture and low bone mineral density in patients with a history of parental fracture

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ABSTRACT

Objectives: Bone mineral density (BMD) and fragility fracture (FF) have high heritability, but few data exist on impact of other factors on families with fracture history. We aimed to evaluate predictors of FF and low BMD, in patients with family history of FF.

Methods: This was a retrospective study on patients undergoing dual energy X-ray absorptiometry at a district general hospital (DGH), 2004–2016. Parameters recorded (in addition to standard dual energy X-ray absorptiometry parameters): age, smoking, alcohol, corticosteroids, aromatase inhibitors, Depo-Provera, hormone replacement therapy, rheumatoid arthritis, polymyalgia rheumatica, breast or prostate cancer, coeliac disease, and fracture site. Logistic regression was used to model fracture risk and site, and linear regression for impact of factors on L1–4 and femoral BMD. Factor analyses with polychoric correlation matrices and calculation of Eigenvalues were applied to determine association between fracture sites and associated risk factors.

Results: A total of 6053 patients were included, 91.1% female. 2094 had sustained at least one FF. Smoking, alcoholism, increased age, height, and fat mass increased FF risk. Sites analysed: femur, tibia/fibula, humerus, forearm, ribs, and vertebrae. Alcoholism, and increasing tissue thickness and fat mass significantly increased FF risk. Decreased right femoral and vertebral BMD increased overall FF risk.

Conclusions: Our study confirms the effect of certain factors on vertebral BMD, but suggests a differential effect on the upper and lower spine, as well as in the dominant and nondominant hip. Different sites of fracture are associated with different risk factors, the most common sites of fracture being the peripheral long bones and vertebrae.

1. Introduction

Fragility fractures (FF) are fractures due to low level ('low energy') force, defined by the World Health Organisation (WHO) as forces equivalent to a fall from standing height or less. Factors known to predispose to FF in the general population include reduced bone mineral density (BMD), systemic corticosteroids [1,2], increasing age, female gender, previous fractures [3,4], menopause [5], and family history of osteoporosis [6]. In the UK, over 300,000 patients present with FF to hospital each year [7]. These cause significant morbidity and disability, and can lead to decreased quality of life and even death [8]. They most commonly occur in the vertebrae, proximal femur and distal radius, and less commonly in the humerus, pelvis, ribs and other bones.

Bone loss increases with age in both men and women, due to age-related factors, and menopause in women, leading to osteoporosis. This is defined as low bone mass with structural loss of bone tissue, increasing susceptibility to FF. The global trend towards an ageing population means the incidence of both osteoporosis and FF is likely to increase. Hip fractures alone are expected to increase in incidence from 91,500 in 2015 to 101,000 in 2020 [7].

While low BMD is an important risk factor for FF, it is important to note that more than half of postmenopausal women sustaining such a fracture do not have osteoporosis [9]. This makes the assessment of other skeletal and nonskeletal factors of clinical importance when assessing fracture risk, as acknowledged by tools such as Fracture Risk Assessment Tool (FRAX®), the most commonly used predictor worldwide.

FRAX® and similar tools provide a 10-year risk of major

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osteoporotic fracture, and hip fracture. An important factor considered when calculating fracture risk is a family history of FF. While several studies have demonstrated the heritability of BMD, and an increased risk of FF in those with a parental history of fracture, independent of BMD, few studies have analysed the effect of other factors in this cohort of patients [6,10]. Additionally, most studies focus on the risk of hip fracture, with little data available on the impact of various factors on FF at other sites, in patients with a history of parental fracture. As outlined above, osteoporosis and associated fractures carry significant morbidity and mortality in the general population. Given the high level of heritability of osteoporosis and decreased BMD, it is important to determine the multiple factors that influence fracture risk in those with a family history of FF.

We set out to analyse predictors of FF and low BMD in patients with a history of parental fracture, presenting for dual energy X-ray absorptiometry (DEXA). Additionally, we analysed predictors of site of fracture and associations between sites.

2. Methods

Patients with a history of parental FF, referred for DEXA scanning at a DGH between 2004 and 2016, were included in the study. DEXA machine and parameters were appropriately calibrated prior to measurement. Parameters recorded were: femoral BMD, vertebral BMD, height, weight, fat mass, lean mass. Additionally, the following factors were recorded: age at scan, history of fracture, smoking status, alcohol consumption, history of corticosteroid therapy, history of aromatase inhibitor therapy, Depo-Provera use, hormone replacement therapy (HRT), history of rheumatoid arthritis (RA), history of polymyalgia rheumatica (PMR), history of breast or prostate cancer, and coeliac disease. For patients with a history of fracture, site of fracture was recorded. Fracture sites recorded were as follows: forearm, tibia or fibula, humerus, femur, ribs, vertebrae.

The statistical software 'R' was used for data analysis. Logistic regression was used to model fracture risk and site of FF, compared to all other FF in the cohort using the above risk factors. The model was adjusted for corticosteroid use due to being a potential confounder for increased risk of fracture. Linear regression was used to model the impact of each of the above factors on BMD at L1–4, femoral neck, and total BMD. Factor analyses with polychoric correlation matrices were applied to determine association between fracture sites. Any associations with Eigenvalues of more than one were then examined using a logistic model to analyse the effect of the above risk factors. Appropriate ethics approval was obtained for this project, in line with the principles embodied in the Declaration of Helsinki. The study was approved by the North West (UK) ethics committee (IRB ethics approval: 14/NW/1136). Consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

3. Results

A total of 6053 patients were included in the study, 5513 (91.1%) female. 2094 (34.6%) had sustained at least one FF. Table 1 summarises the continuous variables used to predict fracture risk in the subsequent tables. Table 2 shows the effect of factors on fracture risk and BMD, adjusted for corticosteroid use. Overall, alcoholism (odds ratio [OR], 1.263; 95% confidence interval [CI], 1.012–1.571), and increasing tissue thickness (OR, 1.017; 95% CI, 1.008–1.026) and fat mass (OR, 6.571; 95% CI, 4.877–8.859) significantly increased FF risk (Table 2). HRT, aromatase inhibitor use, and coeliac disease were found to be protective for FF in this cohort.

Table 3 shows the effect of factors on BMD at the vertebrae and the left and right femur (total and neck only).

A history of breast or prostate cancer, female sex, and increased age significantly decreased vertebral BMD, both at L1–2 and L1–4. There was a differential effect of various factors on right and left femoral BMD, as well as variation according to specific femoral sites. RA, female, and increased age also decreased right femoral BMD; however, left femoral BMD was significantly decreased by none of the factors included in this study.

Table 4 shows factors affecting FF risk at various sites. Sites analysed were: femur, tibia or fibula, humerus, forearm, ribs, and spine. Increased age conferred increased fracture risk at all sites. Increased percentage fact significantly increased fracture risk at all sites except the ribs, with the most significant effect demonstrated in the tibia and fibula. In the peripheral long bones (i.e., forearm and tibia/fibula), fracture risk was significantly increased by female sex, increasing age and increasing percentage fat. RA only increased fracture risk in the femur. The risk of sustaining rib fracture was increased by smoking and alcoholism.

Several factors were found to be protective against FF, as summarised in Tables 3 and 4. Depo-Provera use reduced fracture risk in the vertebrae; coeliac disease reduced fracture risk in the forearm and vertebrae; HRT reduced fracture risk in the forearm, humerus, and vertebrae; aromatase inhibitors reduced fracture risk in all arm bones, tibia and fibula, and vertebrae. Increased height reduced fracture risk throughout the arm and vertebrae, while increased weight reduced fracture risk at all sites except the tibia, fibula, and vertebrae. Increased percentage fat protected against rib fractures. Female gender conferred reduced risk of fracture in the femur, ribs, and vertebrae. Increased BMD in the right femur and L1–2 conferred reduced risk of fracture at all sites except the tibia and fibula.

Polychoric correlation matrices were applied to determine association between fracture sites. Fracture sites with Eigenvalue of

Table 1
Summary of continuous variables.

Parameter	Mean ± SD
Height, cm	162.10 ± 7.59
Weight, kg	69.46 ± 15.56
Average percentage fat, %	0.29 ± 0.07
Average tissue thickness, cm	15.51 ± 2.10
Age at scan, yr	60.59 ± 11.20

SD, standard deviation.

Table 2
Factors predicting fracture risk.

Predictor	OR (95% CI)
Smoking (n = 767)	1.158 (0.985–1.360)
Alcohol excess (n = 357)	1.263 (1.012–1.571)
Rheumatoid arthritis (n = 311)	1.068 (0.840–1.352)
Polymyalgia rheumatic (n = 104)	1.001 (0.660–1.494)
Depo-Provera (n = 73)	1.038 (0.480–2.133)
Coeliac disease (n = 157)	0.575 (0.391–0.826)
History of breast/prostate cancer (n = 77)	0.803 (0.483–1.295)
Female gender (n = 5513)	0.946 (0.788–1.140)
Hormone replacement therapy (n = 388)	0.586 (0.459–0.741)
Aromatase inhibitors (n = 424)	0.489 (0.383–0.618)
Age at scan, yr	1.012 (0.100–1.026)
Height, cm	0.984 (0.980–0.987)
Weight, kg	0.100 (0.998–1.001)
Average percentage fat, %	6.571 (4.877–8.859)
Average tissue thickness, cm	1.017 (1.008–1.026)
BMD- L1–2, g/cm^2	0.113 (0.082–0.155)
BMD- L1–4, g/cm^2	0.122 (0.090–0.164)
BMD- Left femoral total, g/cm^2	0.016 (<0.001–1.589)
BMD- Right femoral total, g/cm^2	0.041 (0.027–0.062)

OR, odds ratio; CI, confidence interval; BMD, bone mineral density.

Table 3
Factors affecting bone mineral density in vertebrae and femur (total and neck).

Variable	L1–2	L1–4	Left femur- total	Left femur- neck	Right femur- total	Right femur- neck
Smoking	1.006 (1.000–1.013)	1.004 (0.997–1.011)	0.986 (0.919–1.059)	1.034 (0.975–1.098)	0.997 (0.992–1.002)	0.999 (0.994–1.004)
Alcohol	1.014 (1.005–1.023)	1.005 (0.996–1.015)	1.195 (1.011–1.413)	1.148 (1.009–1.307)	1.004 (0.997–1.013)	1.006 (0.999–1.014)
RA	1.000 (0.983–1.018)	1.020 (1.001–1.040)	0.897 (0.755–1.067)	0.988 (0.844–1.156)	0.975 (0.960–0.990)	0.981 (0.967–0.995)
PMR	1.038 (1.007–1.071)	1.065 (1.031–1.100)	0.942 (0.700–1.269)	0.914 (0.703–1.189)	1.028 (1.001–1.057)	0.991 (0.966–1.016)
Depo-Provera	1.043 (1.017–1.070)	1.037 (1.010–1.065)	0.893 (0.773–1.033)	NA	1.043 (1.022–1.066)	1.044 (1.022–1.065)
Coeliac disease	0.996 (0.970–1.022)	0.983 (0.957–1.011)	0.879 (0.741–1.044)	0.960 (0.794–1.160)	1.003 (0.982–1.024)	1.016 (0.996–1.037)
History of breast/prostate cancer	0.944 (0.912–0.977)	0.950 (0.917–0.984)	1.001 (0.743–1.349)	0.994 (0.763–1.295)	0.978 (0.950–1.006)	0.982 (0.956–1.008)
Female sex	0.929 (0.914–0.944)	0.932 (0.916–0.948)	0.951 (0.837–1.081)	0.933 (0.847–1.028)	0.931 (0.918–0.944)	0.945 (0.933–0.957)
HRT	1.046 (1.027–1.064)	1.062 (1.043–1.081)	1.112 (0.827–1.496)	1.107 (0.918–1.334)	1.036 (1.021–1.051)	1.039 (1.025–1.055)
Aromatase inhibitors	1.012 (1.005–1.020)	1.013 (1.005–1.021)	0.998 (0.929–1.073)	0.987 (0.908–1.073)	1.012 (1.006–1.019)	1.005 (0.998–1.011)
Age at scan	0.996 (0.996–0.996)	0.997 (0.996–0.997)	0.999 (0.995–1.003)	0.995 (0.992–0.998)	0.995 (0.995–0.996)	0.995 (0.995–0.995)
Height	1.005 (1.004–1.006)	1.005 (1.004–1.006)	1.004 (0.998–1.011)	1.006 (1.001–1.010)	1.004 (1.004–1.005)	1.006 (1.005–1.006)
Weight	1.004 (1.004–1.005)	1.005 (1.004–1.005)	1.006 (1.004–1.008)	1.003 (1.001–1.006)	1.004 (1.004–1.005)	1.004 (1.003–1.004)
Average percentage fat	1.540 (1.483–1.600)	1.530 (1.470–1.592)	1.556 (0.880–2.751)	0.836 (0.499–1.400)	1.091 (1.032–1.154)	0.976 (0.927–1.028)
Average tissue thickness	1.017 (1.016–1.019)	1.018 (1.016–1.019)	1.033 (1.019–1.047)	1.014 (0.998–1.029)	1.030 (1.028–1.031)	1.022 (1.020–1.023)

Values are presented as odds ratio (95% confidence interval).
RA, rheumatoid arthritis; PMR, polymyalgia rheumatic; HRT, hormone replacement therapy; NA, not applicable.

Table 4
Factors affecting fracture site.

Predictor	Fracture site					
	Forearm (n = 1002)	Tibia/fibula (n = 544)	Humerus (n = 235)	Femur (n = 157)	Ribs (n = 272)	Vertebrae (n = 394)
Smoking	0.921 (0.741–1.137)	1.318 (1.021–1.686)	1.219 (0.819–1.764)	1.416 (0.877–2.203)	1.769 (1.264–2.437)	1.119 (0.813–1.514)
Alcohol	1.154 (0.869–1.512)	0.983 (0.660–1.414)	1.594 (0.976–2.470)	1.378 (0.717–2.407)	1.649 (1.042–2.495)	1.296 (0.850–1.901)
A	1.038 (0.758–1.394)	0.920 (0.596–1.361)	1.564 (0.922–2.495)	2.314 (1.333–3.771)	0.770 (0.392–1.356)	1.515 (0.999–2.215)
PMR	1.281 (0.770–2.037)	1.328 (0.687–2.343)	0.732 (0.179–1.963)	1.118 (0.273–3.013)	0.622 (0.154–1.680)	1.037 (0.434–2.091)
Depo-Provera	2.079 (0.906–4.386)	0.699 (0.113–2.328)	<0.001 (<0.001–1.626)	<0.001 (<0.001 –>1000)	0.712 (0.040–3.339)	<0.001 (<0.001 –0.942)
Coeliac disease	0.605 (0.351–0.977)	0.609 (0.287–1.133)	0.476 (0.117–1.265)	0.236 (0.013–1.061)	0.841 (0.328–1.759)	0.369 (0.113–0.878)
History of breast/prostate cancer	0.750 (0.361–1.395)	0.700 (0.245–1.575)	0.657 (0.108–2.104)	0.491 (0.028–2.233)	0.564 (0.092–1.802)	0.579 (0.141–1.560)
Female sex	2.311 (1.709–3.202)	1.421 (1.016–2.050)	1.267 (0.791–2.170)	0.401 (0.270–0.613)	0.671 (0.470–0.989)	0.388 (0.298–0.511)
HRT	0.546 (0.383–0.755)	0.905 (0.612–1.293)	0.438 (0.186–0.867)	0.473 (0.167–1.045)	0.785 (0.433–1.307)	0.521 (0.288–0.863)
Aromatase inhibitors	0.448 (0.311–0.625)	0.486 (0.298–0.748)	0.402 (0.170–0.795)	0.810 (0.381–1.510)	0.711 (0.393–1.183)	0.617 (0.367–0.971)
Age at scan	1.030 (1.027–1.033)	1.019 (1.015–1.023)	1.043 (1.037–1.049)	1.056 (1.048–1.065)	1.008 (1.003–1.012)	1.052 (1.048–1.057)
Height	0.977 (0.973–0.982)	0.998 (0.993–1.004)	0.979 (0.971–0.987)	1.001 (0.990–1.013)	1.003 (0.996–1.010)	0.972 (0.966–0.978)
Weight	0.997 (0.996–0.999)	1.012 (1.010–1.015)	0.994 (0.990–0.998)	0.991 (0.985–0.997)	0.981 (0.977–0.985)	0.997 (0.994–0.100)
Average percentage fat	3.921 (2.710–5.676)	19.619 (12.078 –31.901)	8.365 (4.176–16.758)	2.251 (0.831–6.099)	0.146 (0.078–0.272)	4.613 (2.734–7.789)
BMD- L1–2	0.082 (0.054–0.122)	0.724 (0.447–1.166)	0.169 (0.082–0.343)	0.311 (0.126–0.751)	0.060 (0.030–0.119)	0.162 (0.093–0.282)
BMD- L1–4	0.089 (0.060–0.130)	0.664 (0.418–1.046)	0.140 (0.069–0.281)	0.505 (0.212–1.174)	0.055 (0.028–0.107)	0.127 (0.074–0.215)
BMD- Left femoral total	0.003 (<0.001–0.852)	0.267 (0.0002 –178.120)	0.889 (0.0001 –3070.715)	253.2 (<0.001 –>1000)	145.1 (<0.001 –>1000)	0.007 (<0.001 –>1000)
BMD- Left femoral neck	0.427 (0.0005 –230.984)	0.007 (<0.001 –10.611)	5.144 (<0.001–>1000)	36.651 (<0.001 –>1000)	>1000 (696.5 –>1000)	1.912 (<0.001 –>1000)
BMD- Right femoral total	0.043 (0.026–0.072)	0.678 (0.367–1.246)	0.023 (0.009–0.061)	0.002 (0.0002–0.021)	0.033 (0.014–0.078)	0.042 (0.020–0.085)
BMD- Right femoral neck	0.028 (0.016–0.049)	0.567 (0.291–1.095)	0.032 (0.011–0.092)	0.001 (0.0001–0.016)	0.056 (0.022–0.143)	0.018 (0.008–0.041)

Values are presented as odds ratio (95% confidence interval).
RA, rheumatoid arthritis; PMR, polymyalgia rheumatic; HRT, hormone replacement therapy; BMD, bone mineral density.

more than one (tibia/fibula, vertebrae, ribs) were compared to sites with least covariability (humerus, forearm, femur) (Table 5). These 2 cohorts were significantly different in age; therefore, an age-adjusted model was applied. Smoking (OR, 0.879; 95% CI, 0.779–0.992) and HRT (OR, 0.635; 95% CI, 0.420–0.961) significantly impacted clustering of fractures in the tibia/fibula, vertebrae, ribs, compared with clustering at the humerus, forearm, and femur. Smoking and HRT were found to protect against fractures in the first cluster (tibia or fibula, vertebrae, and ribs), when compared with the second cluster.

Table 5
Age-adjusted predictors of fracture for tibia/fibula/vertebrae/ribs vs. humerus/forearm/femur.

Variable	OR (95% CI)
Smoking	0.879 (0.779–0.992)
Alcohol	0.954 (0.808–1.127)
RA	1.393 (0.928–2.092)
PMR	0.907 (0.465–1.769)
HRT	0.635 (0.420–0.961)
Aromatase inhibitors	0.950 (0.772–1.170)
Breast/prostate cancer	1.489 (0.610–3.636)
Female sex	0.804 (0.589–1.096)
Age at scan, yr	1.011 (1.003–1.019)
Height, cm	0.989 (0.978–1.000)
Weight, kg	0.995 (0.989–1.000)

OR, odds ratio; CI, confidence interval; RA, rheumatoid arthritis; PMR, polymyalgia rheumatic; HRT, hormone replacement therapy.

4. Discussion

4.1. Summary

In this retrospective study on patients with a family history of

fracture, alcoholism and increased fat mass are significant predictors of FF overall. Risk factors for decreased BMD, and risk of fracture, were found to differ between the dominant and nondominant hip. In the presence of pre-existing rheumatological disease, RA significantly decreased right femoral BMD and increased fracture risk in the femur. The most common sites of fracture in this cohort were the peripheral long bones and vertebrae, with significant clustering seen in fractures of the tibia/fibula, vertebrae, and ribs.

4.2. Strengths and limitations

Key strengths of this study include the large sample size, duration over which data was collected, and range of characteristics recorded. We have not only evaluated fracture risk at individual sites, but also association between sites. The population studied is largely homogeneous, with little turnover or variation, strengthening comparative analyses. Limitations of this study include the lack of data on dose and duration of all drugs, including total cumulative dose of corticosteroids. Levels of smoking and alcohol consumptions were not defined within the dataset. Certain clinical factors were also not known, such as proportion of women who were postmenopausal at time of fracture and/or DEXA, as well as fall propensity. Data on treatment for osteoporosis in this cohort was not available, including bisphosphonate treatment, or vitamin D and calcium replacement.

With regards family history, it was not known which parent sustained a fracture. It was also not known at what age parents sustained a FF, or at which anatomical site. This is an important limitation, as genetic factors are believed to be strong determinants of offspring site of fracture and age [11,12]. In the absence of this data, we were thus unable to perform further sensitivity analyses which may reveal the potential differential effect between parental fracture above and below the age of 80 years.

4.3. Predictors of fracture and low bone mineral density

Recent studies show a strong association between parental and offspring BMD, with peak bone mass acquisition more significantly influenced by genetic rather than other factors such as lifestyle and environment. The risk of developing osteoporosis and subsequent fractures is highly dependent on peak bone mass attained [6,13]. These large cohort studies have confirmed heritability of low BMD, but until now, little data has existed on fracture risk, the most important and debilitating complication of the disease.

Similar to studies in the general population, alcohol was found to increase fracture risk [7]. A differential effect of BMD and fracture risk in the dominant and nondominant hip was found. RA and increased age significantly decreased right total femoral BMD and increased femoral fracture risk. These factors conferred no significant effect on left femoral BMD. Certain factors significantly increased right femoral BMD, but not the left, including PMR, HRT, and height. It is not clear as to why there is a differential effect of risk factors on the fracture risk between the dominant and nondominant hips, and may have several explanations, related to the mechanism of injury. One reason may be the mechanism of mobilisation, with patients more likely to weight-bear on their dominant limb. The mechanism of falling is also known to play a key role in the site and severity of subsequent fracture [14]. It is likely that an individual experiencing a fall, regardless of distance fallen, will reach out with their dominant arm to steady themselves as they reach the ground. This will therefore lead to greater impact on the dominant side, thus leading to a greater likelihood of fractures in limbs on this side, including the hip. This may also lead to coexistent fractures of the spine, as well as peripheral long bones, including at the wrist, during the fall.

One key limitation of this study is the lack of data on the treatment of osteoporosis in our cohort. There are comprehensive guidelines [7] available for the treatment of osteoporosis, the most commonly prescribed drugs being bisphosphonates such as alendronic acid [15]. Serum levels of vitamin D, or intake of vitamin D and/or calcium supplementation was also not recorded. This is important for analysis of our results which show coeliac disease to be protective for FF, especially in the forearm and vertebrae. Depo-Provera use and aromatase inhibitors were found to protect against fracture at certain sites. Coeliac disease is known to slightly increase the risk of FF [16], while aromatase inhibitors significantly increase FF risk, especially in women [17]. Depo-Provera use is also associated with a slightly increased risk of fracture [18]. The protective effect seen in the presence of these factors, against FFs, may be due to commencement of bone protection and/or calcium and vitamin D in these patients, which paradoxically reduces their fracture risk. Overall fracture risk was found to be decreased in our cohort across all risk factors, and this may also be due to treatment with bone protecting therapies. This limitation may therefore underestimate the risk of FF in our cohort. However, the study provides further insight into the clustering of fractures, and risk associated with this.

4.4. Predictors of fracture site

In our cohort, different sites of fracture appear to be associated with different risk factors. The most common sites of fracture in this study were the peripheral long bones and vertebrae, with the femur being the least common.

Several studies in literature demonstrate the heritability of fracture risk, more specifically, in a site-specific manner. Fractures of the forearm, especially wrist, have been shown to be particularly common in terms of heritability, in keeping with the results from our study [19,20]. Maternal hip fracture has also specifically been shown to increase the risk of vertebral fracture, especially in men [21]. Within an individual, fractures of the spine, humerus, and pelvis have been demonstrated to increase the risk of further major osteoporotic fracture within the same individual; however, we were unable to analyse this in our cohort due to lack of relevant data [22].

RA significantly increases fracture risk in the femur in our cohort with a family history of FF. This is consistent with results from studies conducted in the general population, which demonstrate RA to positively correlate with increased incidence of vertebral and/or hip fracture [23,24]. A recent systematic review and meta-analysis not only confirmed this result, but also conducted site-specific analyses in RA patients on fractures in the vertebrae, hip, forearm, and proximal humerus. Incidence rates were found to be highest in the vertebrae, leading the authors to suggest vertebral imaging specifically in these patients to assess clinical deterioration of bone structure in the spine, in addition to assessment of other known osteoporotic risk factors, including those specific to RA [25]. This is consistent with previous data, demonstrating vertebral facture rates in RA to be as high as twice the expected value in the general population [26].

4.5. Association between fracture sites

While there is much pre-existing data on the heritability of FF, and preferred sites of FF, little data is available on the association between fracture sites in a given individual. In our cohort of patients, there was overlap between all fracture sites, with significant clustering seen in fractures of the tibia/fibula, spine, and ribs. After adjusting for age, smoking was found to be a significant predictor of

fracture in this cluster, with HRT being protective. This indicates that risk factors for FF are different at different sites, and furthermore, affects the association of fracture between sites, since only these factors were significant for increased FF risk in this cluster.

An explanation for clustering of particular fracture sites, especially those listed above, may be the impact of specific areas of bone loss, such as decreased femoral neck BMD, and areal vertebral BMD, as suggested by one previous study in males [27]. Additionally, as suggested above, fractures may occur at multiple sites during a single fall, dependent on the mechanism of the fall. However, our dataset does not specify the time at which fractures at each site within an individual were sustained; therefore, we are unable to further validate this hypothesis. Further investigations into clustering of fracture sites will enable greater understanding of sites at high risk of fracture in a given individual, thereby directing prevention strategies.

5. Conclusions

This was a study on 6053 patients in a district hospital in North West England, with a family history of FF, presenting for BMD estimation. While this study confirms previous results and risk factors of FF in these patients, it adds to current data by predicting the impact of various clinical factors on fractures at specific sites; little data has previously been available on this. Furthermore, our study demonstrates clustering of certain fractures within these individuals, likely dependent on a certain profile of specific risk factors. Such data may be harnessed to aid fracture prophylaxis and management strategies in patients with a history of FF, protecting against bone loss and FF through mitigation of known risk factors.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest

Mrinalini Dey declares that she has no conflicts of interest. Marwan Bukhari declares the following conflicts of interest: MB has been sponsored to attend national and international meetings by UCB Celltech, Roche/Chugai, Pfizer, Abbvie, Merck, Mennarini, and Eli-Lilly. He has received honoraria for speaking, and has attended advisory boards with Bristol-Myers Squib, UCB Celltech, Roche/Chugai/Pfizer, Abbvie, Merck, Mennarini, Sanofi-Aventis, Eli-Lilly, and Novartis. **ORCID**. Mrinalini Dey: 000-0001-6858-4338. Marwan Bukhari: 0000-0003-4311-5222.

References

[1] Briot K, Roux C. Glucocorticoid-induced osteoporosis. RMD Open 2015;1:e000014.

[2] Allen CS, Yeung JH, Vandermeer B, Homik J. Bisphosphonates for steroid-induced osteoporosis. Cochrane Database Syst Rev 2016;10:CD001347.

[3] Hodsman AB, Leslie WD, Tsang JF, Gamble GD. 10-year probability of recurrent fractures following wrist and other osteoporotic fractures in a large clinical cohort: an analysis from the Manitoba Bone Density program. Arch Intern Med 2008;168:2261–7.

[4] Johnell O, Kanis JA, Odén A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Fracture risk following an osteoporotic fracture. Osteoporos Int 2004;15:175–9.

[5] Gossiel F, Altaher H, Reid DM, Roux C, Felsenberg D, Glüer CC, et al. Bone turnover markers after the menopause: T-score approach. Bone 2018;111:44–8.

[6] Choi HS, Park JH, Kim SH, Shin S, Park MJ. Strong familial association of bone mineral density between parents and offspring: KNHANES 2008-2011. Osteoporos Int 2017;28:955–64.

[7] National Institute for Health and Care Excellence (NICE). Osteoporosis: assessing the risk of fragility fracture. Clinical guideline (CG146). Internet. London: National Institute for Health and Care Excellence; 2012 Aug [cited 2018 Mar 15]. Available from: https://www.nice.org.uk/guidance/cg146/resources/osteoporosis-assessi-the-risk-of-fragility-fracture-pdf-35109574194373.

[8] Sattui SE, Saag KG. Fracture mortality: associations with epidemiology and osteoporosis treatment. Nat Rev Endocrinol 2014;10:592–602.

[9] Aspray TJ. Fragility fracture: recent developments in risk assessment. Ther Adv Musculoskelet Dis 2015;7:17–25.

[10] Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Eisman JA, et al. A family history of fracture and fracture risk: a meta-analysis. Bone 2004;35:1029–37.

[11] Yang S, Leslie WD, Yan L, Walld R, Roos LL, Morin SN, et al. Objectively verified parental hip fracture is an independent risk factor for fracture: a linkage analysis of 478,792 parents and 261,705 offspring. J Bone Miner Res 2016;31:1753–9.

[12] Michaëlsson K, Melhus H, Ferm H, Ahlbom A, Pedersen NL. Genetic liability to fractures in the elderly. Arch Intern Med 2005;165:1825–30.

[13] Kelly PJ, Eisman JA, Sambrook PN. Interaction of genetic and environmental influences on peak bone density. Osteoporos Int 1990;1:56–60.

[14] Palvanen M, Kannus P, Parkkari J, Pitkäjärvi T, Pasanen M, Vuori I, et al. The injury mechanisms of osteoporotic upper extremity fractures among older adults: a controlled study of 287 consecutive patients and their 108 controls. Osteoporos Int 2000;11:822–31.

[15] National Institute for Health and Care Excellence. Bisphosphonates for treating osteoporosis. Technology appraisal guidance [Internet]. London: National Institute for Health and Care Excellence; 2017 Aug [cited 2018 Mar 15]. Available from: https://www.nice.org.uk/guidance/ta464/resources/bisphosphonates-for-treating-osteoporosis-pdf-82604905556677.

[16] Compston J. Is fracture risk increased in patients with coeliac disease? Gut 2003;52:459–60.

[17] Tseng OL, Spinelli JJ, Gotay CC, Ho WY, McBride ML, Dawes MG. Aromatase inhibitors are associated with a higher fracture risk than tamoxifen: a systematic review and meta-analysis. Ther Adv Musculoskelet Dis 2018;10:71–90.

[18] Meier C, Brauchli YB, Jick SS, Kraenzlin ME, Meier CR. Use of depot medroxyprogesterone acetate and fracture risk. J Clin Endocrinol Metab 2010;95:4909–16.

[19] Fox KM, Cummings SR, Powell-Threets K, Stone K. Family history and risk of osteoporotic fracture. Study of osteoporotic fractures research group. Osteoporos Int 1998;8:557–62.

[20] Keen RW, Hart DJ, Arden NK, Doyle DV, Spector TD. Family history of appendicular fracture and risk of osteoporosis: a population-based study. Osteoporos Int 1999;10:161–6.

[21] Diaz MN, O'Neill TW, Silman AJ. The influence of family history of hip fracture on the risk of vertebral deformity in men and women: the European Vertebral Osteoporosis study. Bone 1997;20:145–9.

[22] Morin SN, Lix LM, Leslie WD. The importance of previous fracture site on osteoporosis diagnosis and incident fractures in women. J Bone Miner Res 2014;29:1675–80.

[23] Xue AL, Wu SY, Jiang L, Feng AM, Guo HF, Zhao P. Bone fracture risk in patients with rheumatoid arthritis: a meta-analysis. Medicine (Baltim) 2017;96:e6983.

[24] Hoes JN, Bultink IE, Lems WF. Management of osteoporosis in rheumatoid arthritis patients. Expert Opin Pharmacother 2015;16:559–71.

[25] Jin S, Hsieh E, Peng L, Yu C, Wang Y, Wu C, et al. Incidence of fractures among patients with rheumatoid arthritis: a systematic review and meta-analysis. Osteoporos Int 2018;29:1263–75.

[26] Brennan SL, Toomey L, Kotowicz MA, Henry MJ, Griffiths H, Pasco JA. Rheumatoid arthritis and incident fracture in women: a case-control study. BMC Muscoskelet Disord 2014;15:13.

[27] Chalhoub D, Orwoll ES, Cawthon PM, Ensrud KE, Boudreau R, Greenspan S, et al. Areal and volumetric bone mineral density and risk of multiple types of fracture in older men. Bone 2016;92:100–6.