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ORIGINAL RESEARCH

FRAX assessment in people ageing with HIV

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Abstract

Objectives: Current British HIV Association (BHIVA) guidelines recommend the use of FRAX for the routine assessment of bone fracture risk in people living with HIV over 50 years of age every 3 years. Bone mineral density measurement with dual-energy X-ray absorptiometry (DXA) scan is recommended for those with increased fracture risk (FRAX major > 10%). Our objectives were to estimate the prevalence of and risk factors for osteoporosis in a population of PLWH aged > 50 years and assess the utility of FRAX in predicting the presence of DXA-proven osteoporosis in this cohort.

Methods: This was a cross-sectional study of a cohort of PLWH aged > 50 years attending the Chelsea and Westminster Hospital and who had a DXA scan between January 2009 and December 2018. FRAX scores were calculated using the Sheffield algorithm. Multiple regression models and Cohen's kappa values were used to assess risk factors for osteoporosis and agreement between FRAX and DXA scan results, respectively.

Results: In all, 744 patients were included (92.9% male, mean age 56 ± 5 years). The prevalence rates of osteoporosis (at DXA scans) and osteopenia were 12.2% and 63.7%, respectively. FRAX major was > 10% in only two patients, while 90/91 (98.9%) patients with osteoporosis had a normal FRAX score. The presence of osteoporosis was significantly associated with low body mass index and estimated glomerular filtration rate ($p < 0.05$).

Conclusion: Our results indicate that FRAX scores did not predict the presence of osteoporosis in our population of PLWH over 50 years of age and therefore FRAX scores may not be the appropriate tool to define eligibility to perform DXA scans in PLWH.

KEYWORDS
fracture risk, FRAX, HIV, osteoporosis, PLWH

INTRODUCTION

People living with HIV (PLWH) have a greater prevalence of low bone mineral density (BMD) and osteoporosis compared with age- and sex-matched subjects in the HIV-negative population [1]. The association between HIV infection, low BMD and increased risk of fragility fractures contributing towards significant medical, functional and economic burden has been widely reported [2,3]. Mechanisms leading to bone demineralization in PLWH include direct and indirect effects of HIV, combined antiretroviral therapy (cART) and traditional risk factors, of which some are over-represented in PLWH [4–7]. HIV infection itself may accelerate loss of BMD, through T-cell

chronic activation and inflammatory cytokines that stimulate osteoclast activity [7,8]. Several antiretrovirals, most notably tenofovir diproxil fumarate (TDF) and protease inhibitors (PIs), have been associated with low BMD [9,10].

Current British HIV Association (BHIVA) guidelines recommend routine assessment of fracture risk using Fracture Risk Assessment Tool (FRAX) in PLWH over 50 years of age, postmenopausal women or other high-risk patients every 3 years [11]. Although dual-energy X-ray absorptiometry (DXA) is the gold standard for measuring BMD, DXA is only recommended to refine risk assessment in individuals with elevated FRAX score (10-year risk of major osteoporotic fracture > 10%). By contrast, European AIDS Clinical Society (EACS) guidelines recommend a BMD DXA scan in any person with one or more risk factors (males > 50 years old, postmenopausal women, high risk for falls, history of low impact fracture, symptomatic hypogonadism, steroid use) [12].

Fracture Risk Assessment Tool score, validated by the WHO to establish the 10-year probability of major osteoporotic fractures, is an inexpensive alternative screening tool that can be used routinely in clinical practice. However, FRAX has not been specifically validated in PLWH and may underestimate risk [13]. Low BMD is a strong risk predictor of fragility fractures, especially when associated with known clinical risk factors. Nevertheless, routine measurement of BMD is not affordable in resource-limited settings.

The aims of our study were to estimate the prevalence and risk factors for osteoporosis, and to assess the agreement between FRAX and BMD DXA results and the utility of FRAX in predicting the presence of osteoporosis in a population of PLWH aged over 50 years. Finally, we investigated whether the addition of BMD measurement results and HIV as a risk factor for osteoporosis to FRAX scores changed the clinical management and improved the sensitivity and specificity of current BHIVA guidelines for screening bone diseases in PLWH.

METHODS

Chelsea and Westminster Hospital NHS Foundation Trust (London, UK) runs a dedicated clinic for PLWH over 50 years of age [14]. As part of the routine assessment in our clinic, all PLWH aged > 50 years have an assessment of fracture risk with FRAX and BMD DXA scans every 3 years. We performed a cross-sectional analysis of all DXA scan results available from January 2009 to December 2018 and compared them with the 10-year risk of a major osteoporotic fracture (FRAX major), calculated using the UK version of FRAX algorithm from the University of Sheffield, for each patient at the time of DXA scanning [15]. The FRAX results were obtained without and with inclusion of HIV as a secondary cause of osteoporosis and BMD results, in order to evaluate the usefulness of the tool by using available clinical information. FRAX scores were calculated using BMD results for the femoral neck (FN) as well as the lumbar spine (LS). We used a FRAX major > 10% as cut-off for our agreement analysis, as this is the guideline-recommended threshold to define eligibility to perform DXA scans in PLWH [11,16].

All data were collected into a secured database together with demographic and clinical information. DXA scans were performed using a Discovery A bone densitometer (S/N84395; Hologic, Marlborough MA, USA). According to WHO diagnostic criteria and guidelines for the management of osteoporosis and fragility fracture, osteopenia was defined as T-score was between −1.0 and −2.5 standard deviations (SD), osteoporosis was defined as T-score < −2.5 SD, and severe or established osteoporosis was defined as a T-score < −2.5 SD and by the presence of fragility fractures [17,18]. Vitamin D deficiency was defined as a level < 40 mmol/L. Prevalence of osteopenia and osteoporosis was defined taking into account their presence in one or both sites (FN/LS) for each patient. The study was approved by the Chelsea and Westminster Hospital NHS Foundation Trust as a service evaluation.

Parametric data were presented as mean (SD), and nonparametric data as median and interquartile range (IQR). Univariate and multivariable logistic regression analyses were performed to assess factors associated with: (1) osteoporosis in the spine; (2) osteoporosis in the femur; and (3) osteoporosis in the spine and/or femur. Agreement between FRAX score and DXA results was assessed and data summarized as Cohen's kappa coefficient, sensitivity, and specificity, positive predictive and negative predictive values. Agreement was defined as poor [kappa (κ) < 0.20], fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60) and substantial (κ = 0.61–0.80). Two-sided p-values ≤ 0.05 were considered statistically significant. All statistical analyses were performed using SAS v.9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 744 patients were included in the analysis (92.9% male, 84% of white ethnicity, mean (±SD) age of 56 ± 5 years). Demographic and clinical characteristics of the cohort are summarized in Table 1. The mean (±SD) duration of HIV infection was 15.2 ± 8 years and the mean CD4 count was 660.8 ± 258 cells/μL. The vast majority of patients had an undetectable HIV RNA (714/744; 97.7%) on a stable cART regimen. With regard to past exposure to antiretroviral treatments, 84.1% had been exposed to TDF for a mean (± SD) duration of 5.5 ± 3.1 years, 53.8% had been exposed to PIs for 7.8 ± 5.7 years, and 35.7%

TABLE 1 Baseline demographics of cohort

Characteristic	*n* (%)
Age (years) (mean ± SD)	56 ± 5
Gender	
Male	691 (92.9)
Female	53 (7.1)
Ethnicity	
White	625 (84)
Black	56 (7.5)
Asian	7 (1)
Other	56 (7.5)
Sexuality	
MSM	649 (87.2)
Heterosexual	95 (12.8)
HIV-related parameters Time living with HIV (years) (mean ± SD)	15.2 (8)
CD4 cell count (cells/μL) (mean ± SD)	660 (258)
CD4/CD8 ratio (mean ± SD)	0.98 (3.7)
On cART	727 (97.7)
HIV-RNA < 20 copies/mL	714 (95.9)
Protease inhibitors	400 (53.8)
Time of exposure (years) (mean ± SD)	7.8 (5.7)
Tenofovir exposure	626 (84.1)
Time for the exposed (years) (mean ± SD)	5.5 (3.1)
D-drugs exposure	226 (30.4)
Time for the exposed (years) (mean ± SD)	6.3 (3.8)
Comorbidities	
Dyslipidaemia	373 (50.1)
Hypertension	157 (21.1)
Diabetes mellitus	43 (5.8)
Chronic kidney disease (eGFR < 60 mL/min)	89 (10.8)
Hepatitis B coinfection	24 (3.2)
Hepatitis C coinfection	57 (7)
Weight (kg) (mean ± SD)	79.4 (14.1)
BMI	25.9 (25.4)
Smoking	256 (34.4)
Alcohol intake >14 units/week	90 (12.1)
Vitamin D deficiency (< 40 nmol/L)	184 (24.7)
Low testosterone levels ($n = 691$)	40 (5.8)
Menopause ($n = 53$)	41 (77.3)
History of fragility fractures	11 (1.5)
Corticosteroid use	5 (0.7)
Number of comedications (mean ± SD)	4.9 (2.2)
Polypharmacy	348 (46.8)

Abbreviations: BMI, body mass index; cART, combined antiretroviral therapy; eGFR, estimated glomerular filtration rate; MSM, men who have sex with men.

had been exposed to D-NRTI drugs [didanosine (ddI), stavudine (d4T)]. The presence of clinical risk factors for low BMD in our cohort was as follows – current smoking (256/744, 34.3%), low vitamin D levels (184/744, 24.7%), menopause (41/53, 77.3%) and diabetes (43/744, 5.8%) – while previous history of fractures and low body mass index (BMI) were reported in 2.4% and 1.5% of cases, respectively. Fifty-four subjects out of 744 (7.3%) were on vitamin D supplementation.

Osteoporosis (T-score < −2.5 at any site) was diagnosed in 12.2% (91/744) of patients, with 11.1% (83/744) at the spine and 3.4% (25/744) at the femoral site. The prevalence of osteopenia was 63.7% (41.3% at the spine and 49.2% at the femur). By univariable logistic regression analysis, a statistically significant association was found between the presence of osteoporosis in the spine and a BMI < 20 kg/m^2 ($p = 0.02$) and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 ($p = 0.031$). The association of osteoporosis in the spine with low BMI remained significant in the multivariate model ($p = 0.003$). As for osteoporosis in the femur, we found a statistically significant association with low BMI ($p = 0.004$), years of exposure to PIs ($p = 0.039$) and years of exposure to TDF ($p = 0.030$). Factors independently associated with osteoporosis in the femur in the multivariable analysis were older age ($p = 0.002$) and BMI < 20 kg/m^2 (0 = 0.011).

The vast majority (90/91, 98.9%) of patients with evidence of osteoporosis had a normal FRAX score (FRAX major < 10%) and thus had no indication to perform DXA using current BHIVA guidelines. Calculated FRAX major was > 10% in only two patients, of whom one had osteoporosis. When FRAX was calculated considering both HIV as a risk factor for secondary osteoporosis and BMD results, 15 patients reported a FRAX major > 10% (9/15 with osteoporosis). No patients had FRAX > 20%.

Overall, we found poor agreement between FRAX and DXA results (κ coefficients < 0.2) when using FRAX as a tool to predict the presence of osteoporosis (Table 2). Agreement between FRAX and DXA results improved when FRAX was calculated using BMD and HIV as a risk factor for secondary osteoporosis, achieving moderate agreement ($\kappa = 0.49$) at the femoral site. The sensitivity of FRAX major > 10% for identifying patients with osteoporosis using FN BMD (as recommended by current guidelines) was 50% [95% confidence interval (CI): 1.3–98.7].

The sensitivity of FRAX major >10% for identifying patients with osteoporosis using spine BMD was 50% (95% CI: 1.3–98.7%). The sensitivity to detect the presence of osteoporosis increased to 67% (95% CI: 38.4–88.2) in the femur and to 60% (95% CI: 32.3–83.7) in the spine, when FRAX was calculated with BMD and HIV as a risk factor for secondary osteoporosis.

TABLE 2 Agreement analysis, with sensitivity and specificity, between dual-energy X-ray absorptiometry (DXA) results and FRAX scores, considering 10% as cut-off for abnormal FRAX

	DXA results (spine)		DXA results (femur)	
	No osteoporosis [*n* (%)]	**Osteoporosis [*n* (%)]**	**No osteoporosis [*n* (%)]**	**Osteoporosis [*n* (%)]**
FRAX major				
Normal (< 10%)	660	82	718	24
Not normal (> 10%)	1	1	1	1
	Sensitivity: 50% (95% CI: 1.3–98.7%) Specificity: 89% (95% CI: 86.5% to −91.1) PPV: 1.2% (95% CI: 0.03–6.5) NPV: 99.5% (95% CI: 99.2–100) Cohen's κ: 0.02 (95% CI: −0.02–0.06)		Sensitivity: 50% (95% CI: 1.3–98.7) Specificity: 97% (95% CI: 95.2–97.9) PPV: 4.0% (95% CI: 0.1–20.4) NPV: 99.9% (95% CI: 99.2–100) Cohen's κ: 0.07 (95% CI: −0.06–0.20)	
FRAX major (calculated with HIV and BMD)				
Normal (< 10%)	655	74	714	15
Not normal (> 10%)	6	9	5	10
	Sensitivity: 60% (95% CI: 32.3–83.7) Specificity: 89.9% (95% CI: 87.4–91.2) PPV: 10.8% (95% CI: 5–19.5) NPV: 99.1% (95% CI: 98–100) Cohen's κ: 0.15 (95% CI: 0.06–0.25)		Sensitivity: 67% (95% CI: 38.4–88.2) Specificity: 98% (95% CI: 96.6–98.8) PPV: 40.0% (95% CI: 21.1–61.3) NPV: 99.3% (95% CI: 98.4–99.8) Cohen's κ: 0.49 (95% CI: 0.29–0.68)	

Abbreviations: BMD, bone mineral density; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

DISCUSSION

In this study we aimed at comparing different approaches recommended by both BHIVA and EACS to assessing bone health in PLWH. Current BHIVA guidelines recommend measuring BMD with DXA only in individuals with a FRAX major score > 10%. The results of our study indicate that FRAX may not be the most appropriate tool to define eligibility to perform a DXA scan, as FRAX failed to identify the majority of PLWH with osteoporosis.

Overall, the prevalence of osteopenia in our cohort of older PLWH was 63.7% and that of osteoporosis was 12.2%, more frequently diagnosed in the spine. This is in line with previous reports in the literature, showing a prevalence of osteoporosis in PLWH as high as 15%, more than three times greater than in HIV-uninfected controls of the same age [19]. Risk factors associated with osteoporosis in our study were low BMI, and longer exposure to PIs and TDF, consistent with previous studies [19,20].

Although FRAX is a screening tool developed to predict fracture risk, osteoporosis is a major risk factor for fractures and early diagnosis is crucial to provide lifestyle advice and pharmacological interventions in a timely manner. In line with previous studies that reported poor sensitivity of FRAX both in the general population and in PLWH [20,21], our results confirm that FRAX score should not be used as an only tool to define eligibility to perform DXA. Indeed, if FRAX is used alone, a substantial percentage of osteoporosis diagnoses may be missed. When adding HIV as clinical risk factor for osteoporosis and BMD values, sensitivity of FRAX to predict the presence of osteoporosis improved, mostly at the femoral site.

Limitations of our analysis include the cross-sectional nature of the data collected and lack of long-term follow-up to evaluate the incidence of fractures. Moreover, generalizability of our results may be reduced by under-representation of women and those of non-white ethnicity and therefore may be predominantly applicable to Caucasian males (considering the low number of post-menopausal women, a subgroup analysis would probably not have the statistical power to detect meaningful differences).

The FRAX scores incorporate important risk factors for fragility fractures in order to increase the reliability of identifying individuals most at risk of these types of fracture; however, the use of the FRAX is generally less reliable in PLWH [22]. The FRAX has not been validated in PLWH and there is a concern that the FRAX-derived 10-year risk of fracture may underestimate risk in HIV-infected patients. One of the major potential limitations of use of FRAX in PLWH is that FRAX was initially designed to use the FN BMD to assess fracture risk, while PLWH tend to have a higher prevalence of osteoporosis in the spine [19], as confirmed in our study. The use of the lowest T-score of either the FN or LS to calculate FRAX scores is not the recommended practice in the UK. However, disagreement between the LS and FN BMD measurements on DXA is

often seen in clinical practice, leading to some uncertainty as to how to interpret these results. Several adaptations of FRAX score calculation combining both FN and LS measurements have been examined to evaluate the impact of the disagreement on risk thresholds [23,24]. However, this has not been systematically studied in PLWH.

In conclusion, our results confirm that the FRAX score should not be used as the only tool to define eligibility to perform DXA. Fracture risk assessment using FRAX should be considered in combination with the results of DXA, as the incorporation of clinical risk factors for fragility fractures is important in identifying PLWH with an increased fracture risk and those who will benefit from therapy.

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AUTHOR CONTRIBUTIONS

Maria Mazzitelli collected the data and wrote the manuscript; Pereira Branca Isabel collected the data, and contributed to the final version of the manuscript; Takashi Muramatsu helped in data collection and in the final version of the manuscript; Mimie Chirwa helped in data collection; Ana Milinkovic, Graeme Moyle and Boffito Marta contributed to the study design and to writing the manuscript; Sundhiya Mandalia processed data and performed all statistical analyses. All the authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest in the publication of this paper.

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