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ORIGINAL ARTICLE

High prevalence of radiological vertebral fractures in HIV-infected males

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Abstract Age-related co-morbidities including osteoporosis are relevant in patients responding to combination antiretroviral therapy (cART). Vertebral fractures are common osteoporotic fractures and their diagnosis is useful for managing at-risk individuals. However, there are few data from HIV-infected patients. Therefore, the aim of this study was to determine the prevalence of and factors associated with vertebral fractures in a population of HIV-infected males. A cross-sectional study of 160 HIV-infected patients with available chest X-rays was conducted from 1998 to 2010. One hundred and sixty-three males with comparable age and with no history of HIV infection were recruited as controls. Semi-quantitative evaluation of vertebral heights in lateral chest X-rays and quantitative morphometry assessment of centrally digitized images using dedicated morphometry software were utilized to detect prevalent vertebral fractures. The result showed that the vertebral fractures were detected in 43/160 (26.9%) HIV-infected patients and in 21/163 (12.9%) controls ($P = 0.002$). In HIV-infected patients with fractures, 27 had two or more fractures and ten patients had severe fractures. The prevalence of any fractures and multiple fractures in HIV-infected patients receiving cART (29.6 and 20.0%) was slightly higher than in HIV-infected patients not exposed to cART (17.1 and 5.7%), but significantly higher than control subjects (12.9 and 3.7%). At multivariable analyses, body mass index and diabetes mellitus were independently correlated with vertebral fractures in HIV-infected patients. We concluded that a significant proportion of HIV-infected males receiving cART showed vertebral fractures. Furthermore, proactive diagnosis of vertebral fragility fractures is particularly relevant in patients who are overweight or suffer from diabetes.

Keywords Vertebral fracture · HIV · Antiretroviral therapy · Osteoporosis

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Introduction

Combination antiretroviral therapy (cART) has increased survival in HIV-infected patients. However, several non AIDS related problems emerged, including cardio-metabolic co-morbidities and complications, such as lipodystrophy, obesity, diabetes [1], hypertension [2], metabolic syndrome and insulin resistance [3]. Moreover, osteopenia/osteoporosis and fractures are of concern. The causes of bone complications have not been fully elucidated but could be related to established osteoporosis risk factors [4] (i.e. smoking, opiate use, alcohol use), to the HIV infection per se [5, 6] or to the effect of antiretroviral drugs (in particular, protease inhibitors—PIs and tenofovir—TDF) [7].

Fragility fractures are generally more frequent in HIV-infected populations, and osteoporosis [based on bone mineral density (BMD) measurement] has an overall prevalence of 15% [8–11]. Therefore, screening and prevention strategies based on dual-emission X-ray absorptiometry (DXA) scan have been suggested. However, the mechanisms underlying the possible relationship between BMD, fractures and HIV are yet to be elucidated. Furthermore, in other forms of secondary osteoporosis (i.e. type 2 diabetes)—in which BMD could be normal—BMD measurements may not be the best predictor of osteoporotic fracture risk [12, 13].

Vertebral fractures are thought to constitute a reliable index of osteoporosis complications with significant prognostic value [14]. Data on fragility fractures in HIV-infected patients are scanty and based on retrospective historical assessment of clinical fractures, but this approach unfortunately heavily underestimates these events [10, 15]. Current knowledge support the clinical relevance of radiologically diagnosed vertebral fractures [16] but such evaluation in HIV infection has never been performed. Therefore, the aim of this study was to assess the prevalence of vertebral fractures in a population of HIV-infected male patients and to compare this prevalence with a control population with no diagnosis of HIV infection. Furthermore, possible factors associated with vertebral fractures in HIV-infected patients were investigated.

Patients and methods

A cross-sectional study of 160 male patients infected with HIV was carried out. A database was created using information captured from electronic charts of HIV-infected patients at the Department of Infectious Diseases and chest X-rays in the Radiology Department of the Spedali Civili di Brescia Hospital, Brescia, Northern Italy, from 1998 to 2010. Chest X-rays were selected on the basis of clarity of vertebral images (i.e. absence of overlapping opacities that may confound evaluation of vertebral fractures). When multiple images were available, the last was selected. We selected, as control group, individuals from the following two populations with available chest X-ray images stored at the Radiology Departments: (i) employees who underwent a chest X-ray as part of routine screening procedures at the Spedali Civili (Brescia) and "Carlo Poma" (Mantua) General Hospitals in absence of signs or symptoms of any diseases; (ii) patients admitted to the Spedali Civili (Brescia) Hospital as part of pre-operatory screening for eye-surgery interventions. Also, individuals in the control group had to have an age comparable with that of the cases and had to meet the following exclusion criteria: (1) history of HIV infection; (2) treatment with anti-osteoporotic drugs; (3) treatment with drugs causing osteoporosis and fractures [17]; (4) chronic diseases known to be associated with osteoporosis; and (5) clinical history of recent significant traumas or prolonged immobilization. The control group comprised 163 males (median age, 53 years old, range: 34–71).

Vertebral fractures were detected on lateral chest X-rays using a semi-quantitative evaluation of vertebral heights and quantitative morphometry assessment of centrally digitized images using dedicated morphometry software (Spine-X Analyser ICAM Diagnostics, Milan, Italy). In brief, using a translucent digitizer and a cursor, six points were marked on each vertebral body to describe vertebral shape. Anterior (Ha), middle (Hm) and posterior (Hp) vertebral heights were measured and height ratios (Ha/Hp, Hm/Hp, Hp/Hp of the upper vertebrae, Hp/Hp of the lower vertebrae) were calculated for each vertebral body from T4 to T12; the fractures were defined as mild, moderate and severe on the basis of height ratio decreases of 20–25, 25–40% and more than 40%, respectively [18]. FRAX scores were calculated retrospectively with the online tool using the UK algorithm [19, 20].

Data were expressed as the median and range, unless otherwise stated. Frequencies were compared using Chi-square test, with Fisher correction when appropriate. Un-paired data were compared using the Mann–Whitney test. Logistic regression models were used in the statistical analysis of factors associated with any, severe and multiple vertebral fractures. All factors presented in Table 1 were tested in univariate and multivariable models. Statistical significance was assumed when P values were equal to or less than 0.05.

Results

Patients' characteristics and prevalence of vertebral fractures

Demographic, clinical and viro-immunological data of HIV-infected patients by status of antiretroviral therapy and fractures are presented in Table 1. Overall, the median age of HIV-infected patients was 53 years (range: 42–71) and median duration of known HIV infection was 7.5 years (range: 0.6–25). Thirty-five (22%) patients were naïve to antiretroviral therapy and 125 (78%) were experienced. Patients with vertebral fractures were significantly older ($P = 0.017$), had a higher body mass index (BMI) ($P < 0.001$) and presented with diabetes mellitus ($P = 0.008$) and renal insufficiency ($P = 0.01$) more frequently than HIV-positive patients with no fractures. All patients but seven had a FRAX score $< 4.3\%$ estimated risk of fractures at 10 years which is considered to be the

Table 1 Characteristics of HIV-infected patients

Characteristic ($N = 160$)	Naïve patients ($N = 35$)		Experienced patients ($N = 125$)	
	With fractures ($N = 6$)	Without fractures ($N = 29$)	With fractures ($N = 37$)	Without fractures ($N = 88$)
Qualitative variables (%)				
IVDU	16.7	6.9	36.7	31
AIDS events	83.3	58.6	46.7	55.7
Undetectable VL (copies/ml)	–	–	71.9	64.8
Nadir CD4+ <200 (cell/mm^3)	83.3	72.4	76.7	74.7
BMI (kg/m^2)	50.0	65.5	37.8	63.6
<25.0				
25.0–29.9	50.0	31.0	32.4	29.5
≥30	–	3.4	29.7	6.8
Cigarette smoking	66.7	34.5	54.1	45.5
HCVAb positive	20	10.7	37.8	31.8
Diabetes mellitus	0	3.4	29.7	8.0
Chronic renal insufficiency	0	3.4	18.9	4.5
PI ± RTV exposure	–	–	60.0	59.8
TDF exposure	–	–	38.1	27.4
DDX exposure	–	–	26.7	21.8
Quantitative variables, median (range)				
Age (years)	53 (46–64)	50 (42–54)	54 (45–65)	53 (42–71)
CD4+ cell count (cell/mm^3)	80.5 (8–138)	171 (2–917)	333 (12–742)	316 (4–1,040)
BMI (kg/m^2)	24.7 (18.3–27.0)	24.2 (17.6–32.9)	26.0 (18.6–37.5)	23.0 (14.1–35.8)
Duration cART exposure (days)	–	–	2,211 (126–5,755)	2,376 (70–5,569)

IVDU intravenous drug users, *AIDS* acquired immune deficiency syndrome, *VL* viral load, *Nadir* lowest CD4+ cell count, *BMI* body mass index, *HCVAb* hepatitis C virus antibody, *PI* protease inhibitor, *±RTV* PI with or without ritonavir, *TDF* tenofovir, *DDX* dideoxynucleoside-analogue drugs, *cART* combination antiretroviral therapy

minimum cut-off indicating the necessity of interventions (including DXA scan) regardless patients' age and BMI [19].

Prevalence of vertebral fractures was significantly higher in HIV-infected patients than control subjects (26.9% vs. 12.9%; $P = 0.002$) (Fig. 1). No statistically significant differences in the prevalence of vertebral fractures were evident between patients who were naïve or experienced to antiretroviral therapy (17.1% vs. 29.6%, respectively; $P = 0.14$), but experienced patients had a significantly higher prevalence of fractures than control subjects (29.6% vs. 12.9%; $P = 0.0006$). Furthermore, HIV-infected patients had a higher prevalence of severe and multiple fractures than control subjects, and this difference was predominantly attributed to patients experienced to cART (Fig. 1).

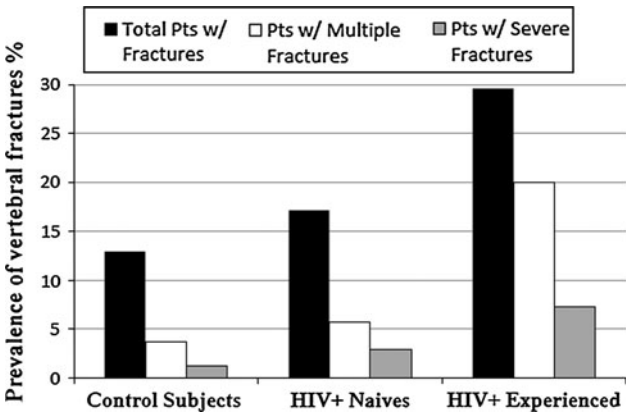

Fig. 1 Any fractures: $P = 0.0006$ controls vs. experienced; multiple fractures: $P < 0.0001$ controls vs. experienced, and $P = 0.07$ for naïves vs. experienced; severe fractures: $P = 0.06$ for Chi-square for trend in experienced vs. naïves vs. controls

Factors associated with vertebral fractures in patients infected with HIV

Three separate logistic regression analyses were performed using any vertebral fractures, severe vertebral fractures and multiple vertebral fractures as dependent variables.

In multivariable analyses, diabetes mellitus was significantly correlated with all outcomes (any fractures: OR = 4.07, 95%CI 1.25–13.48, $P = 0.02$; severe fractures: OR = 8.18, 95%CI 1.30–51.43, $P = 0.02$; multiple

fractures: OR = 6.10, 95%CI 1.48–25.12, $P = 0.01$). For example, vertebral fractures were detected in 61.1% of patients with diabetes co-morbidity and in 22.5% of those without diabetes ($P = 0.003$). Among patients with diabetes mellitus (18 cases), 15 were treated with metformin alone and 3 with insulin plus metformin. Vertebral fractures were not influenced by the antidiabetic therapy (data not shown).

BMI maintained an independent correlation with vertebral fractures (for each unit increase OR = 1.18, 95%CI 1.02–1.35, $P = 0.02$). However, the strongest association was found for BMI $\geq$ 30 kg/m^2 vs. $<$ 25 kg/m^2 with a trend towards significance for the association with severe vertebral fractures (any fractures: OR = 4.5, 95%CI 1.05–19.29, $P = 0.043$; severe fractures: OR = 7.37, 95%CI 0.90–60.78, $P = 0.06$; multiple fractures: OR = 6.44, 95%CI 1.10–37.72, $P = 0.04$).

Age was significantly associated with any fractures in univariate analysis (for each increased year: OR = 1.06, 95%CI 1.01–1.10, $P = 0.01$), but only significantly associated with severe fractures in multivariable analysis (OR = 1.29, 95%CI 1.07–1.57, $P = 0.009$). Chronic renal insufficiency was associated with any fractures only when univariate analysis was carried out (OR = 4.3, 95%CI 1.29–14.38, $P = 0.02$). The other variables were not associated with any outcomes either at univariate or multivariable analyses.

Even after excluding from the group of HIV-positive patients those with diabetes, BMI $\geq$ 30 kg/m^2, clinical diagnosis of liver cirrhosis and smoking habit, the prevalence of fractures resulted significantly higher in the HIV-infected patients than in the controls (8/20 = 40% vs. 21/163 = 12.9%; $P = 0.002$).

Discussion

This study showed that the prevalence of vertebral fractures in HIV-infected male patients was 2.5-fold higher than in a control group of individuals with comparable age. The difference between patients experienced to antiretroviral drugs and the control group was statistically significant and greater than the difference between naïve patients and the controls. The same pattern was evident when the groups were compared in terms of severe and multiple fractures. Even when HIV-infected patients were excluded based on identified risk factors for fragility fractures, the different prevalence in the remaining patients with respect to controls remained significant. Therefore, in our study concomitant co-morbidities as well as HIV infections (either by itself [5] or mediated by systemic inflammation [6]) are associated with increased risk of fractures in HIV-infected patients. Although larger studies should assess the actual prevalence of vertebral fractures in the HIV population (either cART naïve or experienced), our data suggest that this may be higher than expected.

The finding of almost one out of three HIV-infected patients bearing one or more radiological fractures is of potential clinical relevance for several reasons. First of all, it suggests that bone damage is largely more frequent than that assessed in previous studies by BMD measurement (osteoporosis prevalence estimated around 15%) [8–11]. Moreover, the results presented herein may indicate that lateral spine X-rays has a role in the screening algorithms of osteoporosis even before DXA scanning, at least in those with a significant risk of fragility fractures [14]. Interestingly, vertebral fractures occurred in most patients (41/43) without indications to perform DXA scan according to the FRAX algorithm [19]. A lesson we learnt from other forms of secondary osteoporosis, including type 2 diabetes, is that normal BMD alone cannot rule out a risk of fragility fractures as many fragility fractures occur in patients with normal BMD [12, 13]. Furthermore, X-rays are simple to carry out, readily available and cheaper than DXA scan.

Diabetes mellitus emerged as a significant factor associated with fractures in this study, and this is also evident in the general population [21]. Since diabetes occurs in 6–10% of HIV-infected patients receiving cART [22], this is likely to increase the burden of osteoporosis and fragility fractures in ageing HIV-infected patients. Also, overweight patients appeared to have a greater risk of vertebral fractures [23]. This is in contrast to the general population, where low BMI is a risk factor for fragility fractures [24]. An hypothesis to explain this apparent discrepancy is that insulin resistance (even in the absence of overt diabetes) has been associated with alterations in bone metabolism [25]; insulin resistance is frequent in HIV-infected patients, particularly in those with a high BMI [26]; therefore, overweight may be a proxy for insulin resistance and this may justify the association between overweight and vertebral fractures in HIV-infected patients. The association between central adiposity, insulin resistance and bone loss [27] appears to support the previous hypothesis. This possible pathogenic hint warrants further investigations.

Our study has several limitations. First, owing the cross-sectional design we could not assess properly the predictors of vertebral fractures. Second, BMD was not assessed. Third, we did not have any information on gonadal status of our patients; indeed, hypogonadism may complicate HIV infection and it is the main cause of osteoporosis in men [28]. Finally, potential selection bias in our study population may have occurred since inclusion in the study was based on availability of chest X-ray in HIV patients as part of diagnostic work-up for ongoing diseases, so the prevalence of vertebral fractures may have been higher than expected in a general population of patients infected

by HIV. However, among factors that may lead to overestimating the prevalence of vertebral fractures, patients' trauma as indication to perform chest X-ray was not present. Furthermore, the prevalence of vertebral fractures in HIV-infected patients without HIV-co-morbidities was still relevant, suggesting that the risk of radiological vertebral fractures in these patients remained significantly higher with respect to healthy controls.

In conclusion, the results suggest a high prevalence of radiological vertebral fractures in HIV-infected patients. This prevalence was particularly high in, but not limited to, patients with diabetes and those who are overweight. Therefore, these patients should be targeted with screening and preventative strategies. Other factors including age appeared to be less important but this may be a reflection of the cross-sectional design of the present study and the relatively small sample of patients studied. Moreover, the impact of certain antiretroviral drugs (such as TDF) should be assessed further since patients are being treated long-term with these drugs whose impact on BMD has already been demonstrated in short-term studies [29, 30].

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