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TITLE: **“HIV infection and its association with an excess risk of clinical fractures and : a nation-wide case-control study.**

RUNNING TITLE: "**HIV infection and fracture risk.**"

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CONFLICTS OF INTEREST

All the authors declare that they have no commercial or any other association that might pose a conflict of interest for the manuscript enclosed.

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PREVIOUS CONFERENCE PRESENTATIONS

Preliminary results from this work were reported as a Plenary Poster at the last American Society of Bone and Mineral Research (ASBMR) annual meeting, held in Minneapolis (Minnessotta, USA) in October/2012.

Abstract: [179 w]

Background

Different studies have reported an association between HIV infection, antiretroviral therapies and impaired bone metabolism, but data on their impact on fracture risk are scarce. We studied the association between a clinical diagnosis of HIV infection and fracture risk.

Methods

We conducted a case-control study using data from the Danish National Health Service registries, including 124,655 fracture cases and 373,962 age-gender-matched controls. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression.

Results

A total of 50 (0.40/1,000) patients in the fracture group and 52 (0.14/1,000) controls had a HIV diagnosis. The risk of any fracture was thus significantly increased among HIV-infected patients (age and gender-matched OR = 2.89, 95% CI 1.99-4.18). Similarly, significant increases in the risk of hip (OR=8.99, 95% CI 1.39-58.0), forearm (OR=3.50, 95 CI 1.26-9.72), and spine fractures (OR=9.00, 95% CI 1.39-58.1) were observed.

Conclusions

HIV infection is associated with an almost 3-fold increase in fracture risk compared to that of uninfected age and gender-matched uninfected patients. HIV patients are also at an almost 9-fold higher risk of hip fracture.

KEYWORDS: *Epidemiology; HIV; Fractures, Bone; Osteoporosis; Electronic Health Records*

INTRODUCTION

As high active antiretroviral therapy (HAART) for HIV infection allows patients to live longer, many are being confronted with additional health challenges related to ageing [1]. Apart from the classical risk factors, there are morbidities not classically considered to be HIV-related that have been associated with ongoing HIV replication, chronic immune activation, and long-term high activity antiretroviral therapy [1, 2].

In these lines, a number of studies have reported a decrease in bone mineral density (BMD) among HIV-infected patients [1, 3, 4]. A meta-analysis [1] of twelve cross-sectional studies in HIV infected adults found that the probabilities of osteopenia and osteoporosis were 6.4 and 3.7 times higher respectively in HIV-infected than in uninfected patients. However, the consequences of low bone mass on fracture risk among patients diagnosed with HIV infection are not well known, as data is still limited and in some cases contradictory.

We have therefore used the nation-wide Danish health registries to explore the existing association between HIV clinical diagnosis and fracture risk using a case-control design.

METHODS

Setting and source of data

The extensive nature of registers in Denmark covering contacts to the health sector offers good possibilities for studies on the occurrence of fractures [5]. Using the unique 10-digit civil registry number that is assigned to all Danish citizens shortly after birth, a complete hospital discharge and prescription history can be established for each individual, and valid linkage between population-based registries can be obtained. The unique civil registry number is used in all registers, i.e. if a person buys a drug on prescription, the drug is registered as bought by this individual, and the same applies for admissions to hospitals and contacts to general practitioners for reimbursement purposes. Due to the extensive nature of the registers only a few values were missing for socioeconomic status such as civil status, working status and income.

This case-control study was performed within the Danish population that constituted approximately 5.3 million individuals during the study period.

The study was subject to control by the National Board of Health, and the Danish Data Protection Agency.

Study design

This study was designed as a classical case-control study. Cases were all subjects, both genders and all ages, who sustained a fracture during the year 2000. Controls were matched subjects without a fracture in the same year using the criteria below. Exposure was use of drugs and diseases before the date of fracture or a matched index date in the controls. Information on fractures and diseases prior to the fracture was based on hospital records of in- and outpatients.

Identification of fracture cases

In Denmark, The National Hospital Discharge Register covers all contacts (on in- or out-patient basis) to the hospitals [5]. The register was founded in 1977, but outpatient

records were first completely incorporated from 1995. The files of The National Hospital Discharge Register include information on the civil registry number of the patient, date of discharge, and discharge diagnoses, assigned exclusively by the physician at discharge according to the Danish version of the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993, and to the Danish version of the International Classification of Diseases, 10th revision (ICD-10). The register has nationwide coverage of public hospitals with an almost 100% completeness of recordings and a high precision of diagnoses [6, 7], particularly for fracture diagnoses [8]. Using The National Hospital Discharge Register we identified all subjects, who had sustained a fracture between 1 January 2000 and 31 December 2000 (n = 124,655). The following end-points were assessed: any clinical fracture, hip fracture (neck and pertrochanteric), distal forearm fracture, clinical spine fracture, and/or any non-traumatic fracture (any fracture not presenting with an accident mechanism code signalling a trauma of more than a fall at the same level or less as fracture energy). Based on accident codes and admission codes (e.g. hospitalised from home etc.) incident fractures were identified and separated from say re-admissions.

Selection of population-based controls

Using the Civil Registration System, which has electronic records on all changes in vital status, including change of address and date of death for the entire Danish population since 1a68, we randomly selected up to 3 controls for each case, matched by gender, year of birth, and region. The controls were selected using the incidence-density sampling technique (9].

Data on HIV infection

Patients with a diagnosis of AIDS/HIV according to ICD8 code 07983 and ICD10: B20, B21, B22, B23, and B24 were identified from the National Hospital Discharge Register

[10]. Date of HIV clinical diagnosis was accounted for in time-varying models.

Potential confounders

Using The National Hospital Discharge Register [6], we gathered information on the number of days spent in hospital the year preceding fracture [year 1999] and history of a prior fracture in the period 1977-2000. Similarly, data from the National Bureau of Statistics was obtained for a more accurate patient characterisation including: income, social status, working status, and educational status in 1999. The National Health Organisation Register information was then used to study number of contacts to general practitioners and practising specialists for the period 1996 to 2000.

Information on alcoholism was collected as appearance of a diagnosis of alcoholism in the National Hospital Discharge Register or in the Psychiatric Central Register [6], or a prescription of disulfiram in the Prescriptions database. Data on use of drugs with a potential effect on bone metabolism and/or fracture risk [corticosteroids, sedatives, opioids, antidepressants, anticonvulsants, and antipsychotics) were gathered from the Prescriptions database.

Statistical analyses

Data from the different registers were merged at the National Bureau of Statistics, and for each subject the 10 digit civil registry number was substituted by a unique anonymous ID.

The analyses of the association between HIV status and fractures in the year 2000 (cases vs. controls) were carried out using crude and multivariable conditional logistic regression. The latter were adjusted for the following a-priori-defined potential confounders: previous fracture, alcoholism, annual income in the previous year, use of corticosteroids, and sedatives. Further, this logistic model for any fracture was adjusted for use of an a-priori defined list of drugs potentially involved in the causal pathway: opioids, antidepressants, anticonvulsants, and antipsychotics.

In addition, separate analyses for hip, forearm and spine fracture cases and matched controls were also performed using these same methods. Stratified analyses for age strata (young age <40 years, middle age 40 to <60, and elderly >60 years) and gender were carried out, and potential interactions with these were tested for introducing multiplicative terms into the logistic model.

Finally, we studied the effect of time from HIV diagnosis on any fracture risk using a categorical variable for HIV infected patients (up to 2 years, 2.1 to 4 years, 4.1 to 6 years, 6.1 to 7.5 years, and beyond 7.5 years), and fitted a smooth spline plot for visualization of this effect.

All these analyses were performed using STATA 12.0 (STATA Corp., College Station, Tx) and SPSS 19.0 (SPSS Inc., Chicago Ill.). SPSS was used to generate the datasets from raw data and check the completeness of data, while STATA was used for the actual statistical analyses.

Ethics

No informed consent was required for this study, as we used exclusively routinely collected data.

RESULTS

124,655 fracture cases were identified in 2000 in Denmark, and 373,962 controls were matched on age and gender. Hence, both cases and controls had similar age (mean (SD) 43.4 (27.4) years), and 51.8% of both populations were women. Controls had significantly higher annual income, were more likely to be married and actively working, less likely to suffer alcoholism, and to use antiepileptic drugs, sedatives/hypnotics, and corticosteroids. In addition, controls had also less co-morbidities and less commonly a previous fracture history [Table 1].

Prevalence of HIV infection was 0.04% (n=50) among cases and 0.01% (n=52) among controls (p<0.01), equivalent to an overall unadjusted (age and gender-matched) OR of 2.89 (1.99-4.18). Similarly, 3/10,530 (0.03%) hip fracture cases had a previous HIV infection, compared to 1/31,535 (<0.01%) matched controls: OR 8.99 (1.39-58.0). The prevalence of HIV infection among forearm and spine fracture cases was 7/20,035 (0.03%) and 3/3,364 (0.09%), whilst the proportions of HIV infected matched controls were 6/60,030 (0.01%) and 1/10,079 (0.01%) respectively, equivalent to age and gender-matched ORs 3.50 (1.26-9.72) and 9.00 (1.39-58.1) respectively. Adjustment for previous fracture history, alcoholism, use of corticosteroids, use of sedatives and annual income attenuated the observed associations for all but for overall fracture (multivariate adjusted OR 1.99 [1.31-3.03]) [Table 2]. This latter association stood for further adjustment for use of opioids, antidepressants, anticonvulsants, and antipsychotics: OR 1.76 [1.14-2.71].

Stratified analyses by gender demonstrated similarly increased prevalence of HIV among fracture cases in men and women: 45 (0.07%) male and 5 (0.01%) female cases had a history of HIV infection, compared to 48 (0.03%) and 4 (<0.01%) controls. Estimated ORs were therefore 2.73 (1.78-4.19) for HIV-infected men and 3.75 (1.48-9.50) for women with a clinical diagnosis of HIV. Age-stratified analyses offered comparable results in the young

and middle-aged populations (OR 2.76 [1.57-4.86] and OR 3.12 [1.80-5.41] respectively), but no significant increase in HIV prevalence amongst elderly fracture cases: 1(<0.01%) cases aged 60 or older had a history of HIV infection, and 2(<0.01%) controls had an equivalent HIV infection status (OR 1.50 [0.14-16.5]).

The excess risk associated with HIV infection increased with time from diagnosis: for the HIV infected for up to 2 (median 0.84) years, adjusted OR 1.20 [0.53-2.73]; for 2.1 to 4 (median 3.11) years OR 2.30 [1.12-4.72]; for 4.1 to 6 (median 4.98) years 2.10 [1.06-4.16]; for 6.1 to 7.5 (median 6.64) years OR 2.5 [1,14-5,67]; and for >7.5 (median 9.62) years OR 3.00 [1.39-6.47]. According to the smooth spline produced, the effect increases rapidly in the first 2-3 years after the diagnosis of HIV infection to then continue increasing less steeply [Figure 1].

DISCUSSION

We report a significantly increased prevalence of HIV infection of almost 3-fold among fracture cases, compared to gender and age-matched controls from the Danish health registries. This is, in our data, independent of potential confounders, including fracture history, alcoholism, use of potentially involved medications (sedatives, opioids, antidepressants, anticonvulsants, antipsychotics, and corticosteroids), and annual income. Even more importantly, we demonstrate an age and gender-adjusted 9-fold higher risk of hip fractures in HIV-infected patients. Similarly, risk of clinical spine fractures appears to be 9 times higher in patients diagnosed with HIV. A lower effect size (but still significant) effect was observed for the association between forearm fractures and HIV status, with a 3.5-fold increase among the HIV-infected patients. The latter were though attenuated and became non-significant after multivariable adjustment for potential confounders.

The strength of the associations observed between HIV status and fractures is similar for men and women, as well as in younger and middle-aged populations. By contrast, no such relationship was seen among patients aged 60 years or older, possibly because of a reduced number of HIV-infected cases and controls in this strata. In a study by Bonjoch et al male gender was reported as an independent factor for bone loss in HIV patients [11].. Triant et al. where the authors analyzed fracture prevalence amongst HIV and non HIV patients. Instead, we compared the prevalence of HIV in fractured patients versus matched controls [12] .Despite of this, the general conclusions of the study are similar to our findings, where HIV infection and fracture appear to be associated

Most previous reports on the association between HIV infection and fractures studied exclusively American patients. In contrast, our data comes from a Northern European population, with different representation of ethnic groups and probably different risk factors. Nonetheless, the results highlighting an association between HIV infection and

fractures, even, once adjusting for diferent risk factor, are similar.

Finally, we report for the first time a time-varying association between HIV infection and fracture risk: the excess risk associated with HIV infection appears to increase rapidly in the first 2-3 years after diagnosis, and then continues increasing more slowly. Other studies like the one by Yin et al have found that fracture risk is highest in the first 2 years after HAART initiation [13]. Again, whether bone deterioration is consequence of HIV itself or TAR remains controversial.

Despite the evidence of an association between fractures and HIV infection was inconclusive until recently, a number of studies have now consistently pointed to an increased risk in the HIV-infected patients. A just published retrospective cohort study carried out by our group reported similar results, with age and gender-adjusted HRs of 6.2 [95%CI 3.5-10.9; p<0.001] and 2.7 [2.01-3.5; p<0.001] for hip and clinical major fractures respectively among patients from Catalonia (Spain) [14] . Other population-based studies support these findings [12, 15, 16].

Although the causal pathways for such associations remain obscure, different potential factors have been described in the literature. Collin et al demonstrated an increased incidence of all fractures in a cohort of HIV-infected men and women on HAART for ten years [17], raising concerns of undesired effects of HAART on bone metabolism. In a recent study by Womack et al [18] a similar association between fractures and HIV was described, but this was no longer significant after adjustment for body mass index and comorbidities, suggesting that these might explain the increased risk of fractures in HIV populations. Smaller studies, with more restricted samples [4, 19] have suggested that HIV infection is independently associated with BMD reductions in aging men, as well as with increased fracture risk in these patients.

There is therefore a growing body of evidence that indicates that people with HIV are at

high risk for osteoporosis and fractures. However, the pathogenesis responsible for this excess risk remains unclear. Many studies show that the early bone loss seen in HIV patients can be attributed to the use of certain antiretroviral therapies such as protease inhibitors and/or tenofovir [20, 21,22]. In a substudy of 214 patients included in the SMART trial BMD decreased further in the group receiving continous HAART when compared to those on intermittent therapy. More recently, Bedimo et al. have reported on the cumulative effect of continuous tenofovir and lopinavir / ritonavir were on osteoporotic fracture risk [23]. Notwithstanding this, other studies have suggested that the chronic immune activation produced by HIV infection might also play an important role in the development of osteoporotic fractures amongst HIV-infected populations [24, 25]. Various mechanisms might explain the effects of the virus on bone metabolism, including increased production of pro-inflammatory cytokines such as tumor necrosis factor alpha [26] or interleucin 6 [27, 28], and altered vitamin D metabolism in untreated HIV patients, which lead to excessive bone resorption [29]. This narrow interaction between the virus and the patient's immunological status is indeed relevant, as an association between nadir CD4 counts and fractures has been consistently shown [15, 21, 23]. Our study has many limitations, the main one being the scarcity of detailed information on HIV infection and antiretroviral therapies. In addition, we could not investigate other potential confounders such as bone mineral density, smoking, or body mass index. And, HAART medications are not available in this dataset, as these drugs are not dispensed in community pharmacies but in hospital settings. However, we have used highly validated nation-wide data, and our study includes a big and representative sample of patients, with information gathered during routine clinical practice. We also expect low recall bias, as HIV infection is likely to be accurately registered due to the relevant consequences that the coding of this disease has for patients' access to appropriate therapies.

In summary, our study suggests that HIV-infected adults are at an highly increased risk of hip and other bone fractures, compared to the general population. This finding is in line with other recent publications, and adds to a growing body of evidence suggesting that HIV-infected patients should be assessed for fracture risk as part of their routine care.

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TABLES

Table 1: Baseline characteristics for fracture CASES and CONTROLS.

Variable	**Cases (any fracture) n=124,655**	**Controls n=373,962**	**p**
Age (years)	43.44±27.39 (0-100)	43.44±27.39 (0-100)	-
Gender			-
Men	60,107 (48.2%)	180,321 (48,2%)	
Women	64,548 (51.8%)	193,641 (51.8%)	
Annual income (DKR)	161,036±138,789	172,322±193,704	<0.01
Marital status			<0.01
Widowed	18,365 (14.8%)	52,550 (14.2%)	
Divorced	10,423 (8.4%)	23,239 (6.3%)	
Married	35,859 (28.9%)	123,719 (33.3%)	
Unmarried	59,335 (47.8%)	171,349 (46.2%)	
Other#	90 (0.1%)	264 (0.1%)	
Occupational status			<0.01
Independent	3,374 (3.3%)	11,816 (3.9%)	
Assisting wife	209 (0.2%)	951 (0.3%)	
Working	37,797 (36.9%)	124,984 (40.8%)	
Retired	40,201 (39.3%)	109,447 (35.7%)	
Other¤	20,752 (20.3%)	59,278 (19.3%)	
Charlson index*			<0.01
0	97,256 (78.0%)	314,099 (84.0%)	
1-2	19,634 (16.8%)	47,745 (12.8%)	

3-4 ≥5	5,450 (4.4%) 2,315 (1.9%)	9,132 (2.4%) 2,986 (0.8%)	
Previous fracture	41,315 (33.1%)	56,200 (15.0%)	<0.01
Alcoholism	8,863 (7.1%)	9,473 (2.5%)	<0.01
Antiepileptic drugs	7,091 (5.7%)	10,974 (2.9%)	<0.01
Sedatives, anxiolytics, and hypnotics	35,840 (28.8%)	82,766 (22.1%)	<0.01
Ever use of opioids			
Ever use of antidepressants, anticonvulsants, and antipsychotics			
Ever use of any corticosteroid	67,695 (54.3%)	189,636 (50.7%)	<0.01
Ever diagnosed with HIV	50 (0.04%)	52 (0.01%)	<0.01

* A composite index of 19 comorbid conditions (see text), GP: general practitioner. The drugs are ever use from 1996 to 2000 and the diseases prior occurrence of the disease in question between 1977 and 2000. #: Registered partnership, ¤: Not working (students, children etc.)

Table 2: Crude risk of fractures by HIV status

Fracture site	HIV (fracture cases/controls)	Age and gender-matched) OR (95% CI)	Multivariable adjusted OR [ϟ] (95%CI)	Further adjusted for annual income
Any	50/52	2.89 (1.99-4.18)*	2.00 (1.33-3.02)*	1.99 (1.31-3.03)*
Hip	3/1	8.99 (1.39-58.0)*	6.46 (0.61-67.9)	6.93 (0.66-73.2)
Forearm	7/6	3.50 (1.26-9.72)*	2.34 (0.75-7.28)	2.00 (0.61-6.55)
Spine	3/1	9.00 (1.39-58.1)*	4.65 (0.47-46.4)	4.71 (0.47-47.0)

[ϟ] Multivariable OR was adjusted for previous fracture, alcoholism, use of corticosteroids, and use of sedatives

* $p<0.05$

Figure 1. Smooth spline for the effect of time since HIV diagnosis on risk of any fracture.