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A Case-Control Study of Elective Hip Surgery among HIV-Infected Patients: Exposure to Systemic Glucocorticoids Significantly Increases the Risk

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Abstract

Objectives—This was a cross-sectional case-control study amongst a cohort of HIV-infected adults aiming to explore the prevalence of and risk factors for elective hip surgery (total hip arthroplasty and resurfacing).

Methods—Cases were identified from the outpatient database of HIV-infected adults attending one tertiary hospital service. For each case, 5 controls matched by age, gender and ethnicity were identified. From the case notes, information about demographic factors, HIV factors and risk factors for hip surgery due to osteoarthritis or avascular necrosis (body mass index, lipids, alcohol, comorbidities and treatment with oral glucocorticoids) were extracted.

Results—Amongst the cohort of 1900 HIV-infected outpatients, 13 cases (12 male) who had undergone hip surgery (0.7%) were identified, median age 47 years. 11/13 (85%) were Caucasian and 7/13 were in stage 3 of HIV. Significantly more of the control subjects (46% vs. 16%, $p=0.04$) were in the asymptomatic stage of infection. Ever use of oral glucocorticoids was highly significantly associated with elective hip surgery (92% vs. 11%, $P<0.001$).

Conclusions—Amongst this young cohort, the prevalence of elective hip surgery was 0.7% with median age at surgery (47 years) considerably younger than that amongst the general population. Ever exposure to systemic glucocorticoids was highly significantly associated with elective hip surgery, suggesting that the principal mechanism underlying the need for surgery was avascular necrosis. There may be an increased need for elective hip surgery associated with HIV.

Keywords

Elective total hip replacement; hip resurfacing; glucocorticoids; avascular necrosis; osteoarthritis; HIV

Introduction

First performed in 1960, elective total hip replacement (THR) surgery is one of the most effective operations in all of medicine. Annually, an estimated 285,000 are performed in the US and 50,000 in the UK. The principal indications are relief of pain and functional disability (1,2). With careful pre-operative selection, rates of serious complication of <2% are reported even though the mean age at elective hip surgery is 68.5 years. Osteoarthritis (OA) is the most common indication for THR in the general population, accounting for 85% of those undertaken (3). The other most common elective indications are: rheumatoid arthritis and avascular necrosis. Recently, conservative elective hip surgery procedures including resurfacing have emerged as an alternative to THR, particularly in younger patients (7,8), who may require revision later in life.

Since the advent of effective combination anti-retroviral therapy (cART), HIV has been transformed from a fatal illness into a manageable chronic condition. Today, patients with HIV are living long enough to develop chronic degenerative joint disease and require procedures such as total hip replacement. Although there are series published of HIV-infected patients who have received THRs, most have evaluated post-operative infection and/or complications including joint failure (Snir, Capogna, Tornero). Few of these case series have reported the underlying pathology leading to the need for THR. Where data are available, avascular necrosis (AVN) has been identified as a more common indication among HIV-infected cases having hip surgery than among controls (Mahoney, Lubega) but most studies do not report how different aetiologies were distinguished and the underlying pathology was only confirmed histo-pathologically in one study (Mahoney). AVN was first reported in HIV in 1990 (9) but since, it has been suggested that HIV-infected patients have rates up to 40-fold increased compared with the general population (10–12). Avascular necrosis (AVN) is the final common pathway of a number of different conditions all of which lead to interruption of the normal osseous blood supply. Left untreated, it progresses to inadequate healing response, femoral head collapse and a subsequent degenerative arthritis (Lavernia). Traditionally, its management has been purely surgical but non-operative therapy using anti-hyperlipidaemics, antihypertensives, prostacyclin analogues, anticoagulants and bisphosphonates has recently been developing. For example, the results of two recent small studies using bisphosphonates have suggested reduced rates of femoral collapse and need for surgery (Lai, Agarwala), but a third study found negative results (Chen). Therefore an important implication of a delayed diagnosis of AVN is the inability to attempt medical therapy or joint preserving procedures, particularly important in young patients (Pivec).

Femoral neck AVN causes hip pain and/or a limp ('silent hip' disease). Its natural history is poorly researched and it can be self-limiting in some cases ('irritable hip'). Plain radiographs may be completely normal in the early phases and the gold standard diagnostic test is Magnetic Resonance Imaging (MRI) scanning. In the later stages of disease, AVN may be radiographically indistinguishable from hip osteoarthritis causing femoral head collapse (Klippel). AVN may be one of the structural/developmental conditions that predisposes to osteoarthritis. Because of its insidious onset, it is possible that a patient

presenting with hip pain and radiographic osteoarthritis will be referred for hip surgery and not undergo additional investigation with MRI scanning.

Therefore we undertook a cross-sectional study of the prevalence of elective hip surgery among a cohort of HIV-infected adults. Additionally, we used a case-control design in order to explore the risk factors for elective hip surgery in HIV-infected patients.

Methods

Ethical permission for this study was granted by the Brighton Local Research Ethics Committee (10/H1107/72).

This was a case-control study performed November 2010-April 2011. The sampling frame was the database of a large tertiary outpatient centre providing the care for HIV-infected patients. Using the terms 'hip replacement', 'hip resurfacing' and 'hip surgery' the database was interrogated to identify all individuals who had been referred for or undergone hip surgery up until October 2010. For each case, 5 controls were identified, matched for age- (within +/- 5 years; gender and ethnicity). Each control was identified individually using the same database as that utilised for the cases. For each case and control, case notes were reviewed and data extracted about demography and lifestyle factors: age, gender, ethnicity, body mass index (maximum and minimum ever) smoking (current vs ever/never) and alcoholism (ever vs never). HIV data collected were: duration since diagnosis; mode of transmission; CDC clinical stage of infection; nature and duration of cART; viral load; CD4+ nadir and exposure to AIDS defining illnesses. Information was collected about comorbidities and treatments including: lipid abnormalities (most recent values at the time of surgery and highest ever values for cholesterol, triglycerides, high-density lipoproteins (HDLs) and low-density lipoproteins (LDLs)), exposure to megestrol acetate, malignancies, exposure to chemotherapy or radiotherapy and medical treatment with systemic glucocorticoids (defined as documented exposure to oral or intravenous glucocorticoids ever: inhaled and topical glucocorticoids were not included), testosterone and lipid-lowering drugs including statins.

Data were entered into SPSS version 18®. For controls, missing values among continuous data were replaced with the mean value of the remaining 4 controls. For cases, when missing values among continuous data were present, the 5 matched controls were removed from the analysis. No categorical case data was missing. Missing categorical data amongst controls was not replaced, but excluded from analysis. Descriptive statistics were summarised using mean (standard deviation) or median and inter-quartile ranges. Non-parametric data were compared using Pearson's correlation coefficients or Fisher's exact test where indicated. Comparisons between cases and controls for continuous data were analyzed using student's t-tests for matched samples and nonparametric Mann-Whitney U tests. Odds ratios and 95% confidence interval were calculated for risk factors comparing cases with controls.

Results

Amongst a cohort of 1900 HIV-infected outpatients, 13 individuals were identified who had been referred for or received elective hip surgery (prevalence 0.7%) (Table 1). An additional

one patient had received a total hip replacement after a hip fracture and was excluded from this study. Twelve (92%) of the 13 cases were male, 11 (85%) were Caucasian and 2 (15%) were Black African (Table 1). The median age of cases was 47.7 (range 39-56) years. The pre-operative diagnoses from imaging were osteoarthritis among 9 subjects (69%) and AVN among 4 (31%). Nine cases had undergone THR, 6 unilaterally and 3 bilaterally, 2 of whom had bilateral THRs on the same date, and the other at an interval of 4 months. Two individuals underwent hip resurfacing, and 2 cases were awaiting THRs.

There were no significant differences between groups in the proportion that smoked cigarettes or drank excess alcohol. Cases tended towards a longer duration since diagnosis of HIV than controls (12.5 years vs. 9.0 years, $p=0.07$) and significantly more controls were in the asymptomatic stage of HIV infection than cases (46% vs. 16%, $p=0.04$). There was a trend for cases to have a higher maximum mean BMI than controls (28.3 kg/m^2 vs. 26.3 kg/m^2 , $p=0.07$) and to have a greater difference between their maximum and minimum BMI ever (4.8 kg/m^2 vs. 3.1 kg/m^2 , $p=0.06$). Cases were significantly more likely to have ever been exposed to systemic glucocorticoids than controls such that 12/13 cases had been exposed as compared with 7 of 65 controls (92.3% vs. 10.7%, $p<0.0001$). More cases than controls had been treated with chemotherapy (15% vs. 2%, $p=0.07$).

Table 1 summarises the odd ratios and 95% confidence intervals for factors associated with elective hip surgery. Significant risk factors were: exposure to oral glucocorticoid use OR 99.4 (95% CI 11.2-884.5) and exposure to chemotherapy (11.6, 95% CI 1.0-139.5). Being in stage 1 of HIV infection attenuated the risk of having undergone elective hip surgery (OR 0.2, 95% CI 0.0-1.0).

Subsequently, cases were separated according to their preoperative diagnoses into groups of those with radiographic pre-operative osteoarthritis ($n=9$) and AVN ($n=4$) (Table 2). Those factors which remained significantly different between cases with pre-operative osteoarthritis and controls were: difference between maximum and minimum BMI ($p=0.05$), maximum Low Density Lipoprotein (LDL), ($p=0.05$) and exposure to systemic glucocorticoids ($p<0.0001$). Those factors significantly associated with pre-operative radiographic AVN were: exposure to oral glucocorticoids ever ($p<0.0001$) and being in stage 3 of HIV infection (100% vs. 20% of controls ($p=0.007$)).

Discussion

To our knowledge, this was the first ever case-control study evaluating the prevalence of and risk factors for elective hip surgery among a cohort of HIV-infected adults. We found a prevalence of elective hip surgery of 0.7%. This UK-based cohort is relatively homogeneous with 90% male, 90% Caucasian and the majority infected by sexual transmission (predominantly MSMs). At first glance, a prevalence rate of elective hip surgery of 0.7% does not seem extraordinary but, with such a young median age (47 years), those who had undergone elective hip surgery were on average 21 years younger than those in the general population undergoing similar surgery. With the much higher rates of survival since cART and the resultant increasing age of the HIV-infected population, elective hip surgery may become a procedure more commonly required in HIV patients. The majority (9/13, 69%) of

cases had a preoperative radiographic diagnosis of osteoarthritis. Whatever the pre-operative radiographic diagnosis, the most important risk factors for elective hip surgery were: systemic glucocorticoid exposure; body mass index and changes in body mass index, lipid abnormalities and more advanced clinical stage of HIV.

The most surprising finding from this study was the very strong association between exposure to glucocorticoids and hip surgery for radiographic OA (OR 43.4, 95% CI 4.7-403.8). Among the general population, incident OA has been associated with age, body mass index, mechanical factors such as occupational lifting, genetic factors and traumatic or congenital hip damage and glucocorticoids have not been implicated. The likely explanation here is that underlying the radiographic OA at presentation among these HIV-infected patients was in fact AVN. It is well-established that AVN can be incipient and asymptomatic and lead to secondary OA. It appears that, in the absence of a suggestive history, these patients were not investigated for underlying pathology by MRI scanning prior to listing for orthopaedic intervention. This hypothesis is supported by the increasing evidence that AVN occurs more commonly in HIV (11,12). The results of our study suggest that not only is AVN a common underlying diagnosis at the time of hip surgery (confirmed diagnosis in 31%) but also that it is probable that AVN underlies significantly greater numbers of cases requiring hip surgery even amongst those with radiographic osteoarthritis. Highly significant associations with risk factors for AVN were demonstrated amongst cases with radiographic OA whereas the main risk factors for osteoarthritis among the general population were not significantly associated.

Glucocorticoids are well-recognised to be associated with AVN. The mechanism is not as yet understood but may involve hypercoagulability (17) increased rates of cell death and apoptosis through activation of pro-inflammatory cytokines and free radicals (12) or increased fat emboli in femoral blood supply due to secondary hyperlipidaemia (16) or may relate to increased rates of intra-osseous pressure caused by fatty infiltration in bone marrow (16). Many patients with HIV are exposed to glucocorticoids systemically for the treatment of opportunistic infections and, with increasing ageing, will be likely to be exposed for other co-morbidities such as respiratory or rheumatic disease. Until recently, the only recognised treatment options for avascular necrosis were surgical but there has been increasing research to find medical therapies such as bisphosphonates (18), anti-hypertensives, anticoagulants or lipid-lowering agents. To date, there is limited evidence of the efficacy of these approaches, but in the future, it might be that HIV-infected patients requiring systemic glucocorticoids should be co-prescribed agents that might prevent AVN and possibly reduce the risk of future hip surgery.

Femoral neck AVN causes hip pain and/or a limp ('silent hip' disease). Its natural history is poorly researched and it can be self-limiting in some cases ('irritable hip'). Plain radiographs may be completely normal in the early phases and the gold standard diagnostic test is Magnetic Resonance Imaging (MRI) scanning. AVN may be one of the structural/developmental conditions that predisposes to osteoarthritis. Because of its insidious onset, it is possible that a patient presenting with hip pain and radiographic osteoarthritis will be referred for hip surgery and not undergo additional investigation with MRI scanning.

The findings of this study need to be considered alongside several limitations. The methodological approach for this study involved careful case note review and patients were not surveyed directly. It is possible that some cases or controls had been exposed to glucocorticoids prior to enrolment at our Unit. However, this possibility is equally plausible among cases as it is among controls and therefore we feel is unlikely to have caused a systematic bias or on its own explain such highly significant differences between cases and controls.

Hospital case-notes are notoriously inaccurate sources of detailed information about cumulative exposure to glucocorticoids (ref). As such, the study was designed to record exposure to glucocorticoids orally or intra-venously 'ever' from the case-notes. Given that most of the subjects who had undergone hip surgery were reported to have done so for 'osteoarthritis', it was not our primary expectation that glucocorticoids would be identified as such an important risk factor for all participants but rather, this information was collected as a possible confounder likely to be relevant among the patients with AVN. Data collection was undertaken equally rigorously from all case notes, whether cases or controls, since the researchers had no expectation that exposure would play such a significant role. It is therefore highly unlikely that exposure in cases was documented and similar exposure in controls 'ignored'. Cumulative doses and duration of exposure were not collected. Similarly, it was not always possible to identify from the notes the reason for which the patient had been treated with glucocorticoids. Four cases had been treated for pneumocystis carinii pneumonia as part of their acute management and two more as part had received them as part of a chemotherapeutic regimen. In one patient, glucocorticoids had been prescribed long-term for a neuro-ophthalmological diagnosis and another for a rheumatological disease. Clearly, future studies will need to assess nature and duration of glucocorticoids in more detail in order to evaluate what level of exposure is important in future hip disease.

This study was carried out after clinical observation that a relatively high frequency of HIV-infected patients aged <50 years were requiring hip surgery. 13 cases was a relatively conservative number and therefore our statistical power might be limited to find statistically significant risk factors. Where we showed some trends with for example, duration since diagnosis of HIV, a study with higher numbers of cases might have been able to clarify whether this was indeed a true association. It is perhaps even more surprising therefore that we were able to demonstrate such strongly statistically significant relationships with some factors, most obviously systemic glucocorticoids but as a consequence of the small sample size, there are wide confidence intervals. The results of this study need to be replicated in other HIV cohorts.

The role of anti-retroviral therapies in AVN is as yet controversial. The results of some, but not all, studies have suggested that cART and particularly protease inhibitors (PIs) may increase the risk (11–16). Our study explored the duration of cART without finding associations with hip surgery or OA or AVN. Among these small numbers, we had low power to detect any individual effect of one anti-retroviral drug or group of drugs. Further research will be required given the increasing recognition of serious clinical potentiation of effects of glucocorticoids by Ritonavir, a commonly-used PI booster which is metabolised through the same cytochrome P450n as glucocorticoids. The potentiation effects are not

confined to systemically administered glucocorticoids as serious interactions have been documented with inhaled fluticasone (19) and more recently, triamcinolone injected intramuscularly or intra-articularly (20). It is outside the scope of this investigation but it will be important in future research to explore the impact of co-prescribed glucocorticoids and Ritonavir on subsequent risk of AVN and hip surgery.

In summary, this unique case-control study has shown that elective hip surgery has been required on average 21 years younger among HIV-infected adults than in the general population. Avascular necrosis is the pathological process most implicated in the joint destruction even if the radiographic features at presentation are those of osteoarthritis. Systemic glucocorticoids significantly increase the risk of elective hip surgery in HIV-infected adults.

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Table 1
Characteristics of 13 HIV-infected patients requiring elective hip surgery

Case	Gender	Age at surgery	Ethnicity	Mode of acquisition HIV	CDC stage of infection	Radio-graphic diagnosis prior to hip surgery	Elective hip surgery performed or required	Duration of HIV diagnosis at time of surgery (months)	Duration of cART at time of surgery (months)	Exposed to systemic glucocorticoids ever	Reason for exposure to systemic glucocorticoids (where available)
1	M	39	Black African	Heterosexual	C	AVN	Unilateral THR	26.9	26.2	Y	
2	M	48	White Caucasian	MSM	B	OA	Unilateral THR	300.5	96.6	Y	
3	M	42	White Caucasian	MSM	C	AVN	Bilateral THR	157	157	Y	Neuro-ophthalmological
4	M	56	White Caucasian	MSM	C	AVN	Bilateral THR	129.1	127.1	Y	PCP
5	M	47	White Caucasian	MSM	A	OA	Unilateral THR	120.8	72.5	Y	
6	F	47	Black African	Heterosexual	B	OA	Unilateral THR	44.5	44.3	Y	
7	M	45	White Caucasian	MSM	C	OA	Bilateral THR	91.6	12.1	Y	Lymphoma
8	M	43	White Caucasian	MSM	C	AVN	Unilateral THR	288.1	224.4	Y	PCP, chemotherapy
9	M	51	White Caucasian	MSM	C	OA	Unilateral THR	193	147.8	Y	PCP
10	M	51	White Caucasian	MSM	C	OA	Bilateral hip resurfacing	138.2	135.3	Y	PCP
11	M	51	White Caucasian	MSM	B	OA	Awaiting THR	95.7	60.3	Y	Rheumatological
12	M	53	White Caucasian	MSM	B	OA	Awaiting THR	196.5	137.9	Y	
13	M	44	White Caucasian	MSM	A	OA	Unilateral hip resurfacing	198.3	136.4	N	N/A

Table 2
Comparison of demographics, HIV factors and exposure to therapies between 13 cases who had undergone elective hip surgery and 65 age-, gender- and ethnicity-matched controls

Characteristics	Cases (n = 13)	Controls (n = 65)	Univariate comparisons <i>p</i> value	OR	95%CI
Median (IQR) age (years)	47 (43.5-51)	48 (43.5-51)	1.00		
Gender (Number male, %)	12 (92%)	60 (92%)	1.00		
Ethnicity (Number White British vs. other)	11 (85%)	55 (85%)	1.00		
Cigarette smoker (ever)	10 (77%)	33 (54%)	0.13		
Excess alcohol drinker	1 (8%)	4 (6%)	0.84		
Highest ever BMI mean (SD)(kg/m ²)	28.8 (3.5)	26.6 (4.7)	0.14		
Lowest ever BMI mean (SD) (kg/m ²)	23.2 (3.7)	22.7 (3.8)	0.66		
Mean difference between maximum and minimum BMI (kg/m ²)	5.5 (3.8)	3.9 (2.8)	0.09		
HIV Factors					
Transmission route (Number MSM vs. other, %)	11 (85%)	52 (80%)	0.70		
Median (IQR) duration of HIV diagnosis (years)	12.5 (6.8)	9.0 (6.1)	0.22		
Median (IQR) duration of HAART (years)	8.7 (5.0)	7.1 (4.6)	0.51		
Mean (IQR) CD4+ nadir (cells/μl)	187 (623)	217 (844)	1.00		
Clinical stage of infection					
Stage 1	2 (16)	29 (45)	Ref		
Stage 2 or Stage 3	11 (84)	36 (55)	0.05		
Lipid abnormalities					
Maximum mean (SD) cholesterol (mmol/L)	7.7 (2.5)	6.3 (1.5)	0.06		
Maximum mean (SD) TG (mmol/L)	5.8 (6.1)	4.0 (3.0)	0.33		
Maximum mean (SD) LDL (mmol/L)	4.9 (1.6)	3.9 (1.2)	0.01*		
Minimum mean (SD) HDL (mmol/L)	1.0 (0.6)	0.9 (0.5)	0.68		
Exposure to therapy					
Systemic steroid use ever	12 (92)	7 (11)	< 0.001*		
Testosterone use ever	3 (23)	4 (6)	0.051		
Statin use ever	6 (46)	14 (22)	0.064		
Chemotherapy ever	2 (15)	1 (2)	0.018		
Radiotherapy ever	0 (0)	2 (3)	0.522		

Table 3
Comparison of demographics, HIV factors and exposure to therapies between 13 cases with preoperative diagnosis of (a) osteoarthritis and (b) avascular necrosis and 65 controls

Characteristics	OSTEOARTHRITIS			AVASCULAR NECROSIS		
	Cases (n = 9)	Controls (n = 45)	p value	Cases (n = 4)	Controls (n = 20)	p value
Median (IQR) age (years)	48.3 (5.0)	49.8 (5.9)	0.92	42.8 (12.6)	42.7 (12.3)	0.90
Gender (Number male, %)	8 (89%)	40 (89%)	1.00	4 (100%)	20 (100%)	-
Ethnicity (Number White British vs. other)	8 (89%)	40 (89%)	1.00	3 (75%)	15 (75%)	1.00
Cigarette smoker (ever)	7 (78%)	23 (54%)	0.27	3 (75%)	15 (75%)	1.00
Excess alcohol drinker	1 (11%)	3 (7%)	0.53	0 (0%)	1 (5%)	1.00
Mean (SD) maximum BMI (kg/m ²)	28.8 (3.9)	26.0 (4.2)	0.07	27.8 (-)	26.1 (5.9)	0.37
Mean (SD) minimum BMI (kg/m ²)	23.8 (3.2)	22.3 (3.8)	0.27	24.5 (-)	22.4 (3.8)	0.86
Median (IQR) change in BMI (kg/m ²)	5.0 (2.6)	3.1 (2.2)	0.05*	3.3 (-)	3.0 (2.1)	0.77
HIV Factors						
Transmission route (Number MSM vs. other, %)	8 (89%)	37 (82%)	1.00	3 (75%)	15 (75%)	1.00
Median (IQR) duration of HIV diagnosis (years)	12.6 (6.3)	9.4 (6.4)	0.18	11.7 (16.7)	8.4 (10.0)	0.31
Median (IQR) duration of HAART (years)	7.7 (4.0)	7.7 (4.5)	0.98	11.7 (12.8)	5.2 (7.2)	0.14
Mean (IQR) CD4+ nadir (cells/μl)	194 (554)	212 (585)	0.77	172 (623)	229 (844)	0.31
Clinical stage of infection						
Stage 1	2 (22%)	19 (42%)	0.46	0 (0)	10 (50%)	0.11
Stage 2	4 (44%)	7 (16%)	0.07	0 (0)	6 (30%)	0.54
Stage 3	3 (33%)	19 (42%)	0.72	4 (100%)	4 (20%)	0.007*
Lipid abnormalities						
Maximum mean (SD) cholesterol (mmol/L)	7 (5)	6 (2)	0.06	8 (4)	7 (2)	0.60
Maximum mean (SD) TG (mmol/L)	4 (6)	3 (3)	0.96	5 (4)	4 (4)	0.25
Maximum mean (SD) LDL (mmol/L)	5 (4)	4 (1)	0.05*	5 (3)	4 (2)	0.46
Minimum mean (SD) HDL (mmol/L)	1 (1)	1 (0)	0.11	1 (1)	1 (0)	0.06
Exposure to therapy						
Systemic steroid use ever	8 (89%)	7 (16%)	<0.001*	4 (100%)	0 (0%)	<0.001*
Testosterone use ever	2 (22%)	3 (7%)	0.53	1 (25%)	1 (5%)	0.31
Statin use ever	4 (44%)	8 (18%)	0.10	2 (50%)	6 (30%)	0.58
Chemotherapy ever	1 (11%)	1 (2%)	0.31	1 (25%)	0 (0%)	0.17
Radiotherapy ever	0 (0%)	2 (4%)	1.00	0 (0%)	0 (0%)	-