Avascular necrosis of the femoral head in HIV positive patients-an assessment of risk factors and early response to surgical treatment

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Abstract

26 consecutive patients (37 hips) with avascular necrosis (AVN) of the femoral head treated surgically at our institution from 1999 to 2008 were reviewed . The aims of the study were to evaluate the risk factors associated with AVN in HIV positive and HIV negative individuals, and assess early response to total hip replacement (THR) surgery in HIV positive and negative patients. There were 15 male and 11 female patients in total. The mean age for all patients was 47.1± 8.0 years (range, 33 to 66 years). 12 patients were HIV positive, 11 patients were HIV negative and 3 patients had unknown HIV status. Excessive alcohol intake was the most common risk factor for developing AVN .15 patients (58%) had more than one risk factor for AVN and only 2/12 (17%) HIV positive patients had no other risk factor apart from HIV infection. There were no early postoperative complications in 34 arthroplasties in both HIV positive and negative patients. The aetiology of AVN seems often to be multifactorial, even in the presence of HIV infection. Early response to arthroplasty surgery in AVN of the femoral head is equally good irrespective of the HIV serostatus of the patients.

Introduction

Avascular necrosis (AVN) of the femoral head, also known as osteonecrosis, is a condition in which there is cell death of various bone components including haematopoietic fat marrow and mineralised tissue. The estimated incidence of AVN in the general population is 0.135%[1,2]. There are several aetiological factors that may result in AVN. Risk factors for osteonecrosis can be divided into traumatic and non traumatic. Traumatic causes include fractures and dislocations. Non-traumatic causes include: systemic steroids, alcohol abuse, hyperlipidemia, hypercoagulability, sickle cell disease, smoking, Gaucher's disease, collagen vascular disease, deep sea diving, pregnancy, pancreatitis and irradiation. In 8-20% of AVN cases, no association with the known risk factors has been noted[1].

AVN of the femoral head is an emerging condition in HIV infected patients[1-5,7,8,10,11,13]. Whether osteonecrosis is an HIV-related complication, an adverse effect of antiretroviral (ARVs) therapy or is caused by another HIV associated condition remains unclear[5]. The reported estimated incidence of AVN in HIV patients ranges from 0.45 to 1.33%[5-9] which is greater than in the general population. Some authors have attributed the increasing incidence to hypertriglyceridaemia, which is frequently seen in HIV positive patients. Hypertriglyceridaemia secondary to use of protease inhibitors has also been reported[1,7,8].

The HIV prevalence rate among adults in Malawi is 11.9%[14]. There have been some reports in the infectious diseases and HIV/AIDS literature about the development of AVN in HIV positive patients. However, we found only 2 reports relating to HIV and AVN in the orthopaedic literature[13,16], one of which was pertaining to outcome of surgical intervention, but not indexed on a Medline search.

Avascular necrosis of the femoral head, traumatic and non-traumatic, is the leading cause of total hip joint replacement (THR) in Malawi, accounting for 53% of the cases[17]. It is not clear what proportion of non-traumatic AVN patients are HIV positive. No study has been done to assess the risk factor profile of AVN patients in Malawi and the association between HIV infection and AVN. In addition, it is not known whether early response to hip replacement surgery is different between HIV positive and negative patients. Thus this study set out to assess for other risk factors of AVN in HIV positive patients and see if the association may be multifactorial; explore the alleged association of AVN and ARVs; and assess the early response to hip replacement surgery.

Methods and Materials

All patients with non-traumatic avascular necrosis of the femoral head who underwent a total hip replacement surgery between 1999 to 2008 were identified from the National joint registry database[17]. The study duration was chosen to assess the first 10 years of the joint registry. THR which involves prosthetic replacement of both the acetabulum and the femoral head, is the definitive treatment for patients with advanced AVN. In addition 2 patients who had avascular necrosis of the femoral head and were treated at our institution by core decompression in the same time-period were also included in the study.Core decompression surgery is done in patients with early AVN (pre-collapse stage), during which the necrotic femoral head is drilled to decompress the increased intraosseus pressure in the femoral head and neck of patients with AVN thereby improving blood supply. One patient had total hip replacement (THR) in one hip, and core decompression in the other . Thus all patients receiving surgical treatment for AVN were included. This maximised numbers for risk factor evaluation, but assessment of outcome of surgery was restricted to total hip replacement patients to keep the group homogenous.

The diagnosis of AVN was made clinically and using plain radiographs because plain radiography was the only imaging technique available in Malawi during the study period. Core decompression was done if there was no collapse or fragmentation of the femoral head, whereas THR was done if there was fragmentation, collapse or secondary degenerative changes of the hip joint and the clinical symptoms warranted THR. All the patients in the study had no symptoms and signs suggestive of sickle cell disease. The National joint registry records all cases of joint replacement in Malawi. It had a total of 67 patients (81 total hip replacements) from 1999 to 2008. Approval from the local ethics committee was obtained and individual informed

consent was obtained from each patient in the study group.

The study group provided data on all AVN patients coming to surgery, and allowed comparison between HIV positive and negative patients in terms of AVN risk- factor profile and outcome after surgery. The group consisted of 26 patients, who underwent a total of 34 primary total hip arthroplasties and 3 core decompressions.

Data on patient characteristics, risk factors for avascular necrosis, HIV status, ARVs, and follow up were extracted from the National joint registry database using a proforma. The medical records and the x-rays of these patients were also reviewed. Risk factor profile data that was not available in the medical records and the database was obtained from the patients at the time of this analysis, either through telephone or direct interview. Assessment of early response to THR surgery was done by comparing pre-operative and post-operative Harris Hip score, a well known score in orthopaedics used to assess hip function and pain. In addition we reviewed the registry for documentation of any major complications such as deep venous thrombosis, early sepsis and dislocations.

Consent was obtained to collect blood samples to check non fasting cholesterol and triglyceride levels, as this is not routine in the registry. We assumed that abnormal levels of cholesterol and triglyceride in the blood are likely to remain elevated if not treated and none of the patients in the study were on special diets or cholesterol lowering drugs; thus all lipid profiles were taken at the time of this analysis.

Patients were considered as having hypercholesterolemia if the serum total cholesterol was > 200mg/dl and hypertriglyceridemia if the serum triglyceride level was> 200mg/dl. The reference levels were given by the laboratory that measured the blood samples.

Alcohol intake was considered a risk factor for males if the weekly consumption was >37.5 units within 2 years before the onset of symptoms of AVN [18]. No female admitted to taking alcohol. Oral steroids were considered as a risk factor if the patient had taken about 1800 mg prednisolone or an equivalent over 4 weeks[19].

With regard to statistical analysis, all statistical analyses were done using SPSS 16.0 statistical program. Hypothesis testing was done using Fisher's chi-squared test for categorical variables and Man-Whitney U test for continuous variables. Seroprevalence of HIV in AVN patients was compared with seroprevalence in the general population using two sample test of proportion.The level of statistical significance was $p<0.05$ for all statistical analyses.

Results

Patient Characteristics

Table I shows baseline characteristics of the study patients. There were 15 males and 11 females. The mean age of the patients in the study group was 47.1± 8.0 years (range, 33 to 66 years). There were more obese patients (BMI>30) in the HIV seropositive group than in the seronegative group, however the difference in the mean BMI was not statistically significant (p= 0.141).

HIV Seroprevalence, Use of ARVs, HIV stage and CD4 count

In our study 88.5% (23/26) of the AVN patients were tested for HIV, and 46% of them were HIV seropositive. Given that the background population seroprevalence is 11.9%[14], the seroprevalence is 4 times higher among the AVN patients compared to the general population. This difference was statistically significant ($p<0.001$).

Five patients had symptoms before and 7 patients had symptoms after starting antiretroviral drugs. Only 3 patients were taking protease inhibitors as part of their regimen at the time of first symptoms of AVN. Only 2 patients whose symptoms developed after they had started taking ARVs had no other known risk factors.

More than half of the HIV seropositive patients (7/12) had a diagnosis of AVN when the clinical stage of HIV/ AIDS was quite advanced (see figure 2). Data on CD4 counts at the time of AVN diagnosis was available in 7 patients. Four patients had a CD4 count between 200- 499 cells/ul (normal is >1000cells/ul) at the time of AVN diagnosis (Table 2).

Table 1: Baseline Characteristics of Study Participants

Total number of patients (n)	26 (37 hips)
Gender distribution	
Males	15
Females	11
Mean age (years)	47.1 ± 8.0
HIV Serostatus	
Positive	12
Negative	11
Unknown	3
Mean BMI	
HIV seropositive	30.7 ± 5.6 (p= 0.141)
HIV seronegative	26.8 ± 5.9
Mean Pre op Harris Hip Score	
HIV seropositive	24.3 ± 11.8 (p=0.495)
HIV seronegative	27.9 ± 8.8
Surgical intervention	
THR (No. of hips)	
HIV seropositive	15
HIV seronegative	16
Unknown HIV serostatus	3
Core Decompression (No. of hips)	
HIV seropositive	2
HIV seronegative	0
Unknown HIV serostatus	1

Table 2: CD4 count at the time of AVN diagnosis (known in 7/12 HIV patients

CD4 count (cells/ ul)	Number of patients
≥500	2
200 – 499	4
< 200	1

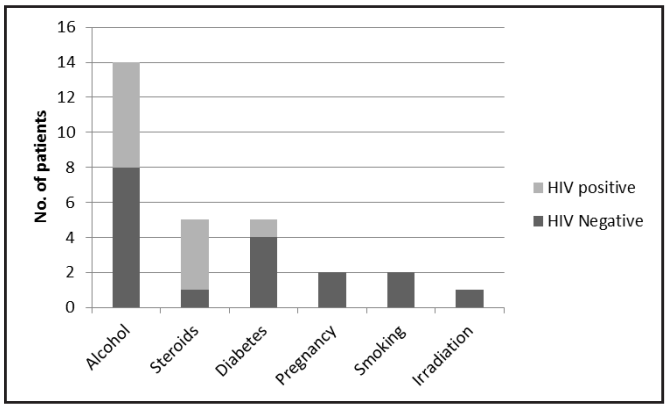
Table 3: HIV Serostatus and Anatomical distribution of AVN

AVN sites	Negative	Positive	Unknown	Total
1hip	4 (36)	3 (25)	1	8
2hip	7 (64)	8 (67)	2	17
Multifocal	0	1 (8)	0	1

Risk Factors

The most common risk factor in the study group was excessive alcohol intake accounting for 12/26, 2 patients started having symptoms suggestive of AVN while they were pregnant (Figure I). More than half of the patients had more than one risk factor for AVN and only 2 patients out of 12 HIV positive patients had no other risk factors (Figure I). Figure I also shows the numbers of patients in separate risk factor groups who were HIV positive.

Figure 1: Risk factors of Avascular Necrosis



We managed to check cholesterol and triglyceride levels in 9 HIV positive and 10 HIV negative patients. The mean cholesterol level in HIV seropositive and seronegative patients was 190.0 mg/dl ± 47.80 and 183.7mg/dl± 37.5 respectively. The mean triglyceride levels in the HIV seropositive and seronegative patients were 144.0mg/dl ± 71.3 and 129 mg/dl ± 81.4 mg/dl respectively. These differences were not statistically significant (p= 0.604). The serum total cholesterol levels were elevated in 4/9 HIV positive patients and 3/10 HIV negative patients. The serum triglyceride levels were elevated in 4/9 HIV positive patients and in 2/10 HIV negative patients.

There was no statistically significant difference in the anatomical distribution of AVN sites between the seropositive and seronegative groups (p= 0.4) (Table 1). One patient in the seropositive group had multifocal disease involving both hips and both shoulders.

Early response to surgery:

Only three patients had core decompression compared to 23 patients who had 34 total hip replacement operations. For the arthroplasty patients, the mean pre operative Harris hip scores were 24.3± 11.8 and 27.9± 8.8 in the HIV positive and negative groups respectively. This difference was not statistically significant (p= 0.495). The mean post operative Harris Hip Score at 6 months to one year in the HIV seropositive and seronegative groups were 82.9 ± 3.9 and 84.9 ± 8.5 respectively. Again this difference was not statistically significant (p= 0.9). The median prosthetic duration in those patients who had a total joint replacement was 36 months (range 0 to 96 months).

There were no major complications like deep venous thrombosis, early sepsis, dislocations or late sepsis. There were no patients lost to follow up. There was one death, in an HIV positive patient who died of AIDS-related complications 8 years after arthroplasty.

Discussion

Many have observed an association between HIV disease and AVN, but a causal link or indeed a discrete mechanism has not been defined. This study has shown an association between HIV disease and AVN of the hip (p<0.001).

However, we only found two articles on this subject in the orthopaedic literature [13,16] where as they were several in infectious disease literature, thus it seems most orthopaedic surgeons are unaware of the association between HIV and AVN. Many standard orthopaedic texts and web sites do not mention it, whilst mentioning some very rare risk factors[20-22]

The reported proportion of idiopathic AVN among AVN patients ranges from 8- 20%. In our study 11.5% had no known risk factors for AVN. Fifteen (57.7%) had more than one risk factor for AVN and only 2 patients out of 12 HIV positive patients had no other risk factors apart from HIV infection. This finding supports a concept that the aetiology of AVN may frequently be multifactorial including in the presence of HIV infection. The most common risk factor for the development of AVN in our study group was excessive alcohol intake. Four out of five patients who had used steroids were HIV positive. Steroids are used in the management of a number of HIV related conditions. The pathology of steroid and alcohol induced AVN is not very clear but it has been suggested that they may cause fatty infiltration of the bone marrow thereby compromising blood supply[1,11,12]. They may also promote fat embolism within the bone vasculatur[e1,12]. Our findings agree with what other studies have already found that certain risk factors are more prevalent in HIV positive patients[1,2].

The suggested aetiology of AVN in HIV positive patients includes hypertriglyceridaemia and altered lipid metabolism. This would be consistent with a synergistic effect between alcohol or steroids and HIV seropositivity. In neither group were mean levels above the normal range, but there were a few patients in both groups whose lipid levels were above the normal range. This calls for another study with a larger sample size and controls from the normal population.

Several authors have alluded to an association with ARVs and more specifically protease inhibitors [5, 7-10, 23,27]. Only 3 patients out the 7 who had symptoms after they started taking ARVs were taking a protease inhibitor at the time of AVN diagnosis in our study. We managed to check lipid levels for only one out of these three patients, and the levels were normal. The suggested mechanism, by which protease inhibitors may be implicated in the aetiology of AVN in HIV positive patients, is due to induction of hyperlipidaemia [2,3,5-8,]. Scribner et al found saquinavir to be associated with the development of AVN. However the findings in our study show that protease inhibitors are not solely responsible for AVN. In fact, case reports of AVN in HIV positive patients began to appear in the literature before the advent of these drugs[1, 2, 6, 7, 9, 10].

One of the limitations of our study was lack power because of the relatively small sample size and lack of a control group, thereby making it difficult to make definite conclusions. There is therefore need for a case control study in future to mitigate these limitations., However there are still some important findings that should be considered.. Our study, like other studies, demonstrates a multi-factorial aetiology of AVN in HIV infected patients, but does not give evidence of a causal link between HIV and AVN. It is an important finding of this study to highlight this area of uncertainty so that future studies can define whether the effect is causal or simply an association.

It may be that HIV disease sensitizes an individual to the

effect of alcohol or steroids in causing AVN. Alternatively, HIV could be associated with other risks that are known to cause AVN such as excessive alcohol consumption and steroid use. On the other hand, several authors have described a significantly greater proportion of HIV positive patients with no other known risk factors compared with HIV negative patients[7,10,13].

In our study, 7/12 patients presented with symptoms of AVN at WHO clinical stage III. Data on CD4 counts at the time of AVN diagnosis was available in 7 patients. Six of these patients had a CD4 count of >200 cells/ul. It is difficult to draw any conclusions from this data but some studies have suggested that AVN can occur at any level of immunosuppression[5,7].

There were no major complications following THR surgery in both HIV positive and negative patients. There was also no significant difference between the groups, in the pre and post-operative Harris hip score checked at six months to one year post total hip replacement. This indicated an impressive symptomatic improvement. In the South African study on hip arthroplasty in HIV-infected patients, all their patients were given rifampicin for 9 months as to prevent bacterial adherence to implants[16]. The use of antibiotics may have been considered to contribute to the lack of postoperative infection in their study patients. Our paper also reports a zero early infection rate after arthroplasty , but without resorting to long-term prophylactic antibiotics. The findings in our study suggest that early response to THR surgery is good whether the patient is HIV positive or negative. The absence of early infection and other complications is consistent with our studies on outcome after internal fracture fixation in HIV positive patients with closed injuries[9,24]. At present we are not aware of any report of medium to long- term outcome of arthroplasty in HIV except those with haemophilia[25]. We are unsure whether or not results in haemophiliacs translate to other HIV positive patients as discussed previously[24,26]. We have demonstrated that patients with HIV associated AVN can get good early results after total hip replacement in terms of pain relief, function and low complication rate, but we cannot yet comment on medium to long-term results.

This study indicates that HIV disease is associated with AVN of the hip , but the aetiology of AVN may be multifactorial even in the presence of HIV infection. Thus in our unit we have now made counseling and HIV testing part of the routine investigation of all non-traumatic AVN cases.

There is need for a large study to establish the role of hyperlipidaemia and other risk factors in AVN patients, particularly those who are HIV seropositive.

All orthopaedic surgeons should be aware of the association between HIV and AVN of the femoral head, and should consider counseling and testing for HIV in their routine investigation of the disease.

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