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Original Article

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Osteonecrosis of the Femoral Head in Korean Patients with Human Immunodeficiency Virus Infection

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ABSTRACT

Background: Osteonecrosis of the femoral head (ONFH) is a disabling condition that often necessitates total hip arthroplasty (THA). Although ONFH occurs more frequently among patients with human immunodeficiency virus (HIV) than among the general population, there is little epidemiological information regarding ONFH in Korean patients with HIV. In the present study, we aimed to investigate the incidence and clinical features of ONFH among Korean patients with HIV.
Materials and Methods: In this retrospective study, we reviewed the medical records of 1,250 Korean patients with HIV treated from January 1990 to December 2019. A standardised data collection sheet was used to obtain clinical information. Imaging data were analysed by a radiologist in accordance with the 2019 revised version of the Association Research Circulation Osseous (ARCO) staging system for ONFH.
Results: Among the 1,250 included patients, 13 patients (1.04%; 3 women, 10 men) were diagnosed with ONFH. The overall incidence of ONFH was 1.29 per 1,000 person-years (PYs) (95% confidence interval [CI]: 0.7 – 2.4 per 1,000 PYs). Median age among the 13 patients with ONFH was 47 years (interquartile range [IQR]: 41 – 57 years). The median duration since HIV diagnosis was 4.8 years (IQR: 2.3 – 10.1 years). The median CD4 cell count at the time of ONFH diagnosis was 381 cells/ mm^3 (IQR: 161 – 551 cells/mm^3). At the initial diagnosis of ONFH, 83.3% of patients exhibited bilateral involvement. ARCO stage 3 or 4 osteonecrosis was observed in 83% of patients. Among 22 hips, stage 1 ONFH was noted in 2 (9.1%), stage 2 ONFH was noted in 7 (31.8%), stage 3 ONFH was noted in 9 (40.9%), and stage 4 ONFH was noted in 4 (18.2%). THA was eventually performed in 84.6% of patients. Five (38.5%) patients had a history of steroid use, 4 (30.8%) patients had a history of alcohol abuse and 10 (76.9%) were smokers. Eight (61.5%) patients had a history of acquired immune deficiency syndrome-defining illness, including 7 with tuberculosis and 1 with pneumocystis pneumonia. Nine patients (69.2%) had a nadir CD4 cell count <200/μL, and 3 (23.1%) had a history of bone fracture. Overall, 84% of patients were exposed to antiretroviral therapy, while 54% had taken protease inhibitors for more than 1 year.

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Conflict of interest
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Author Contributions
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Conclusion: Considering that relatively high incidence of ONFH in patients with HIV, a high index of suspicion for those with risk factors and those with groin or hip pain for is required in HIV-infected patients.

Keywords: Osteonecrosis; Femoral head; Hip; HIV

INTRODUCTION

Osteonecrosis of the femoral head (ONFH) is a disabling condition that leads to collapse of the femoral head, frequently necessitating total hip arthroplasty (THA). ONFH generally affects patients between the ages of 30 and 50 and can thus can lead to significant disability in the most productive years of life [1, 2].

Human immunodeficiency virus (HIV) infection has been associated with an increased risk of developing ONFH. The estimated incidence of ONFH among patients with HIV ranges from 0.03 to 0.37 cases per 100 person-years (PYs), which is up to 100-fold higher than the estimated incidence among the general population [3]. However, the pathophysiology of ONFH in patients with HIV remains poorly understood. Some studies have suggested that HIV itself increases the risk of ONFH development, while others have highlighted the potential roles of corticosteroid use, hyperlipidaemia, hypercoagulable states, alcohol abuse, smoking, and adverse effects of antiretroviral therapy (ART) [3-6].

Although early diagnosis and appropriate intervention can delay the need for joint replacement, treatment success is related to the stage during which care is initiated. ONFH is a slowly progressive disease that can be difficult to recognise due to its nonspecific initial symptoms. As such, most patients present with advanced ONFH [1, 2]. Furthermore, among new presentations, 18.75% of cases are diagnosable only via magnetic resonance imaging (MRI) and are easily missed on normal radiographs [7]. Asymptomatic ONFH is also common among patients with HIV. In previous longitudinal studies, 4.4% of asymptomatic patients with HIV exhibited signs of ONFH on MRI, and an additional 1.7% of those with negative MRI results developed ONFH within 5 years [3, 8]. Therefore, an improved understanding of the incidence and clinical presentation of ONFH in patients with HIV may allow for earlier diagnosis and enhance prevention efforts.

In Korea, the estimated annual prevalence of ONFH in the general population is 28.91 cases per 100,000, based on a study that utilised 5-year national health insurance claim data from 2001 to 2006 [9]. However, there is little epidemiological information regarding HIV infection in Korean patients [10]. In the present study, we aimed to investigate the incidence and clinical presentation of ONFH among Korean patients with HIV.

MATERIALS AND METHODS

In this retrospective study, we analysed the computerised medical records of patients with HIV who had visited Pusan National University Hospital, Korea from January 1990 to December 2019. Patients under the age of 18 at the time of enrolment and those of non-Korean ethnicity were excluded. Those who had first visited for non-HIV-related care and were subsequently lost to follow-up were also excluded. Medical records were reviewed using

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a standardised data collection sheet. Patients were classified as having a history of alcohol abuse if the patient's clinician noted heavy alcoholic use, which is defined as consuming an average of ≥4 drinks per weeks on the chart [11]. Imaging data were analysed by a radiologist in accordance with the 2019 revised version of the Association Research Circulation Osseous (ARCO) staging system for ONFH [1, 12]. The Institutional Review Board of Pusan National University Hospital approved the study protocol and waived the requirement for informed consent due to the retrospective nature of the study (IRB No. 2004-019-090).

The incidence of ONFH was calculated by dividing the number of cases of ONFH by the total number of PYs of observation. The observation period extended from the date of the first visit to the study hospital to the earliest of the following dates: the date of ONFH diagnosis, the date of death, the date of the last follow-up visit in cases of transfer or loss to follow-up, or December 31st, 2019. SPSS version 21.0 (IBM Inc., Chicago, IL, USA) was used for statistical analyses.

RESULTS

A total of 1,325 patients with HIV-1 infection visited the study hospital between 1990 and 2019. Among them, 41 patients of non-Korean ethnicity, 2 patients under the age of 18, and 32 patients lost to follow-up after non-HIV-related first visits were excluded. Thus, a total of 1,250 patients (median age: 42 years; interquartile range [IQR]: 33 – 51; 89.2% male) (**Table 1**).

Among the 1,250 included patients, 13 (1.0%) were diagnosed with ONFH. Of the 13 patients with ONFH, 3 had received a diagnosis of ONFH before presenting to the study hospital. One patient had already undergone bilateral THA 8 and 13 years after HIV diagnosis due to ONFH, respectively. Two patients were transferred to the study hospital for surgery, and one of them was diagnosed with HIV during the preoperative evaluation for THA.

Table 1. Baseline characteristics of 1,250 patients with HIV

Variables	Numbers (n = 1,250)
Median age in years (IQR)	42 (33 - 51)
Male	1,115 (89.2)
Sexual orientation	
Heterosexual	636 (50.8)
Homosexual/bisexual	569 (45.5)
Unknown	45 (3.6)
Marital status	
Unmarried	630 (50.4)
Ever married	597 (47.8)
Unknown	23 (1.8)
Comorbidities	
Diabetes	147 (11.8)
Hypertension	153 (12.2)
HBV seropositive	96/1,135 (8.5)
HCV seropositive	54/1,083 (5.0)
Median CD4 cell count (IQR)	241.5 (64 - 391)
Duration from presentation to care	
1990 - 1999	144 (11.5)
2000 - 2009	581 (46.5)
2010 - 2019	525 (42.0)

HIV, human immunodeficiency virus; IQR, interquartile range; HBV, hepatitis B virus; HCV, hepatitis C virus.

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Of the remaining 1,247 patients, 10 developed ONFH during the observation period. The total observation period encompassed 7,732.5 PYs, and the overall incidence of ONFH was 1.29 per 1,000 PYs (95% confidence interval [CI]: 0.7 – 2.4 per 1,000 PYs).

The demographic and clinical characteristics of the 13 patients diagnosed with ONFH are shown in **Table 2**. There were 3 women (23.1%) and 10 men (76.9%), with a median age of 47.5 years (IQR: 42.5 – 57 years). The median duration since HIV diagnosis was 4.8 years (IQR: 2.3 – 10.1 years). The median CD4 cell count at the time of ONFH diagnosis was 381 cells/mm^3 (IQR: 161 – 551 cells/mm^3). Seven patients (53.9%) were current smokers, and 3 (23.1%) had smoked previously. Four patients (30.8%) had a history of alcohol abuse.

Table 2. Demographic and clinical characteristics of 13 patients with HIV diagnosed with ONFH

Variables	Numbers (n = 13)
Male	10 (76.9)
Median age at ONFH diagnosis in years (IQR)	47 (41 - 57)
Median time from HIV diagnosis to ONFH diagnosis in years (IQR)	4.8 (2.3 - 10.1)
Median time since ART initiation to ONFH diagnosis in years[a] (IQR)	4.7 (3 - 8.8)
ART use (>1 year)	
NRTIs	11 (84.6)
NNRTIs	2 (15.4)
PIs	7 (53.9)
INSTIs	3 (23.1)
None	2 (15.4)
Comorbidities	
Cardiovascular disease	2 (15.4)
Diabetes	2 (15.4)
Depression	2 (15.4)
Gout	1 (7.7)
Smoking	
Never	3 (23.1)
Ever	10 (76.9)
Steroid use	
Ever (>3 weeks)	5 (38.5)
At the time of ONFH diagnosis	2 (15.4)
Alcohol abuse	4 (30.8)
Osteopoenia/osteoporosis on bone mineral density (T score -1 or lower)	6 (46.2)
Prior history of bone fracture	3 (23.1)
Prior AIDS-defining illness	
Tuberculosis	7 (53.9)
Pneumocystis pneumonia	1 (8.3)
Prior CD4 cell count <200 cells/mm^3	9 (69.2)
Median CD4 cell count at the ONFH diagnosis[b] in cells/mm^3 (IQR)	381 (161 - 551)
Bilateral involvement at the first diagnosis of ONFH[c]	10/12 (83.3)
ARCO stage ONFH diagnosis[c] (among 12 patients[d]/among 22 hip joints)	
1	0 (0) / 2 (9.1)
2	1 (8.3) / 7 (31.8)
3	8 (66.7) / 9 (40.9)
4	3 (25) / 4 (18.2)
Total hip replacement	
Unilateral	4 (30.8)
Bilateral	7 (53.9)

[a]Among 11 patients receiving ART prior to ONFH diagnosis.
[b]Among 12 patients with CD4 cell count data.
[c]Among 12 patients with imaging data.
[d]The most advanced stage in cases of bilateral joint involvement.
HIV, human immunodeficiency virus; ONFH, osteonecrosis of the femoral head; IQR, interquartile range; ART, antiretroviral therapy; NRTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, non-nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; AIDS, acquired immunodeficiency syndrome; ARCO, Association Research Circulation Osseous Staging System of Osteonecrosis of the Femoral Head.

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Overall, 5 patients (38.5%) had received corticosteroids for more than 2 weeks at some point during the observation period. Two patients (15.4%) were receiving corticosteroids at the time of ONFH diagnosis. Eight patients (61.5%) had a history of acquired immunodeficiency syndrome (AIDS)-defining illness, including 7 with tuberculosis and 1 with pneumocystis pneumonia. Nine patients (69.2%) had a nadir CD4 cell count <200/ mm^3. Three patients (23.1%) had a history of bone fracture.

Among the 13 patients with ONFH, 11 patients (83%) were receiving ART at the time of ONFH diagnosis. The median time from initiating ART to ONFH diagnosis was 4.7 years (IQR: 3 – 8.8 years). Classes of antiretroviral drugs to which patients were exposed for more than 1 year included the following: nucleoside analogue reverse transcriptase inhibitors (NRTIs) in all 11 (84.6%) patients, protease inhibitors (PIs) in 7 patients (53.9%), integrase strand transfer inhibitors (INSTIs) in 3 patients (23.1%), and non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) in 2 patients (15.4%).

Among the 12 patients with imaging data, 10 (83.3%) exhibited bilateral involvement of the hip joint at initial diagnosis of ONFH. In 9 of these patients, one hip was more severely affected than the other. Among the 22 affected hips, stage 1 ONFH was noted in 2 (9.1%), stage 2 ONFH was noted in 7 (31.8%), stage 3 ONFH was noted in 9 (40.9%), and stage 4 ONFH was noted in 4 (18.2%). Overall, 10 patients (83.3%) were initially diagnosed with advanced ONFH (stage 3 or 4). Of the 13 patients with ONFH, 11 (84.6%) underwent THA after a median of 54.5 days (IQR: 24.3 – 167.8 days) from ONFH diagnosis, while 7 also underwent THA of the opposite hip after a median of 357 days (IQR: 14 – 623 days).

DISCUSSION

In the present study, we investigated the incidence and clinical presentation of ONFH in Korean patients with HIV. Our analysis revealed that the overall incidence of ONFH among patients with HIV was 1.29 per 1,000 PYs.

The reported incidence of ONFH among patients with HIV varies across studies, depending on the study population, the duration of observation, rates of comorbidities, and ART use. Such studies have reported rates of 0.3 to 3.7 cases per 1,000 PYs [3, 5, 13-18], which is up to 100-fold higher than the estimated incidence in the general population [3, 19]. In accordance with our findings, a recent large-scale international cohort study involving more than 11,000 patients with HIV reported an ONFH incidence of approximately 1 per 1,000 PYs [17]. Although no reports have documented the annual incidence of ONFH in the general Korean population, the annual prevalence of ONFH is 28.91 per 100,000 [9]. Despite these differences, the incidence of ONFH among patients with HIV in our study was significantly higher than the estimated incidence in the general Korean population.

Although several risk factors have been linked to an increased risk of ONFH in patients with HIV, the results of these previous studies should be interpreted with caution, given their small sample sizes. One case-control study involving patients with HIV in the United States (17 with ONFH, 34 controls) identified corticosteroid use as an important risk factor for ONFH [19]. In addition, a French study including 104 patients with HIV (83 with ONFH) demonstrated that prior AIDS-defining illness, low CD4 cell counts, and exposure to ART were significantly associated with osteonecrosis [5]. A study conducted in Spain further reported that 87% of

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54 symptomatic patients with HIV and osteonecrosis had at least 1 identifiable risk factor, the most common of which included dyslipidaemia, alcohol abuse, use of corticosteroids or megestrol acetate, antiphospholipid antibodies, and local trauma [16]. In a recent large-scale cohort study including 89 cases of ONFH, prior AIDS-defining conditions, low CD4+ T-cell counts, Caucasian race, and a history of prior fracture/prior osteonecrosis were associated with an increased risk of ONFH [17]. Although some studies have linked exposure to ART (including PIs) to an increased risk of ONFH, others have failed to observe this association [17, 20]. In our study, 92.3% of patients had at least 1 previously suggested risk factor for ONFH. Overall, 38.5% of patients had a history of steroid use, 30.8% of patients of patients had a history of alcohol abuse, and 76.9% were smokers. Approximately 60% had a history of AIDS-defining illness, including tuberculosis and pneumocystis pneumonia, while 69.2% had a nadir CD4 cell count <200/mm^3. Furthermore, 23% had a history of bone fracture, 84% were exposed to ART, and 54% were exposed to PIs for more than 1 year.

Treatment of ONFH is based on the disease stage. The mainstay of treatment is surgical using either a joint-preserving procedure, if possible, or total hip arthroplasty. Joint-preserving procedures are more successful in the early stage of disease when the femoral head is still salvageable. If ONFH has progressed to the advanced femoral head collapse, THA is a more reliable treatment [21, 22]. However, early diagnosis of ONFH remains challenging, as the symptoms and imaging characteristics are insidious and subtle. Most patients present late in the disease course [1, 2]. In our study, 83.3% of patients were initially diagnosed with late-stage ONFH (ARCO stage 3 or 4), and 83.3% presented with bilateral ONFH at initial diagnosis. No patient underwent joint preserving surgery, and 84.6% eventually underwent THA. Few other reports have commented on ARCO stage at the initial diagnosis of ONFH in patients with HIV. However, one recent study involving 413 patients with ONFH-including 14 with HIV-reported that nearly 80% of patients presented with late-stage ONFH [22]. Of the 14 patients with HIV, 71.4% were diagnosed with advanced-stage ONFH (ARCO stage 3 or 4), similar to our findings. Another previous study reported that 50% of 22 patients with HIV and ONFH presented with late-stage ONFH (stage 3, 4, or 5 based on the Steinberg classification scheme) [6].

Although routine screening for ONFH is not recommended among asymptomatic patients with HIV, our findings suggest that a high index of clinical suspicion of ONFH is necessary for earlier detection in those with known or probable risk factors, such as steroid use, alcohol abuse, smoking. It also seems prudent to recommend earlier MRI of the hips for patients with early symptoms referable to the hip [22].

The present study possesses several limitations of note. First, this was a hospital-based, retrospective observational study. The collection of epidemiological information regarding risk factors such as coagulopathy, hyperlipidemia may have been limited due to the retrospective nature of our study. Therefore, we cannot rule out the presence of unmeasured confounding factors. Second, our study was conducted at a single centre. Although our institution is among the largest HIV/AIDS care centres in the south-eastern region of Korea, only a small number of ONFH cases were included. Therefore, caution should be exercised when attempting to generalise our results to other regions of the country, and multicenter prospective studies may be needed in future. Third, the incidence of ONFH may have been underestimated because ONFH was diagnosed only in symptomatic patients.

Care should be taken when obtaining the patient's clinical history in order to identify and modify any risk factors for ONFH. In addition, educational strategies designed to improve

the patient's understanding of the anticipated course of ONFH are also recommended. Our findings ultimately support the notion that a multidisciplinary approach involving physicians, radiologists, and orthopaedic surgeons is necessary to ensure early diagnosis of ONFH in patients with HIV.

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