High Prevalence of Osteonecrosis of the Femoral Head in HIV-Infected Adults

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Background: Osteonecrosis has been reported to occur occasionally among HIV-infected patients. The diagnosis of symptomatic osteonecrosis of the hip in two of the authors' patients, together with reports from community physicians, raised a concern that the prevalence of osteonecrosis is increasing.

Objective: To determine the prevalence of osteonecrosis of the hip in asymptomatic HIV-infected patients and to identify potential risk factors associated with osteonecrosis.

Design: Survey and comparison study.

Setting: The Clinical Center of the U.S. National Institutes of Health.

Participants: 339 asymptomatic HIV-infected adults (of 364 asked to participate) and 118 age- and sex-matched HIV-negative volunteers enrolled between 1 June and 15 December 1999.

Measurements: Osteonecrosis of the hip, as documented by magnetic resonance imaging. Data from clinic records and a patient questionnaire administered before magnetic resonance imaging were used in an analysis of risk factors. A subset of patients was evaluated for hypercoagulable state.

Results: Fifteen (4.4% [95% CI, 2.5% to 7.2%]) of 339 HIV-infected participants had osteonecrosis lesions on magnetic resonance imaging, and no HIV-negative participants had similar lesions. Among HIV-infected participants, osteonecrosis occurred more frequently in those who used systemic corticosteroids, lipid-lowering agents, or testosterone; those who exercised routinely by bodybuilding; and those who had detectable levels of anticardiolipin antibodies.

Conclusions: Patients infected with HIV have an unexpectedly high occurrence of osteonecrosis of the hip. Although screening asymptomatic patients is not warranted, HIV-infected patients with persistent groin or hip pain should be evaluated for this debilitating complication.

The natural history of HIV infection has changed substantially with the widespread use of highly active antiretroviral regimens that include potent protease inhibitors or non-nucleoside reverse transcriptase inhibitors (1). The incidence of HIV-related deaths and HIV-associated opportunistic infections has decreased dramatically. As survival and quality of life have improved, the focus of health care providers has shifted to management of the increasingly complex drug regimens and their associated drug interactions and toxicities. Previously unrecognized or underrecognized complications related to HIV infection or therapies for HIV infection, such as lactic acidosis, hyperlipidemia, and fat redistribution, are increasingly being recognized (2).

Osteonecrosis of the hip (also known as avascular necrosis) is a disabling condition that frequently requires total hip replacement (3–5). Osteonecrosis in HIV-infected patients was first reported in 1990 (6). Subsequent anecdotal reports have suggested that osteonecrosis is being diagnosed with increasing frequency in the setting of HIV infection (7–31). Between May 1999 and November 2000, six HIV-infected patients followed at the Warren Grant Magnuson Clinical Center of the U.S. National Institutes of Health (NIH) presented with groin or hip pain and received a diagnosis of osteonecrosis. The first two of these patients received their diagnosis within a 4-day period and were the first HIV-infected patients ever to receive such a diagnosis at the NIH Clinical Center. We also learned that an increasing number of cases of osteonecrosis were being reported to the U.S. Food and Drug Administration’s Adverse Event Reporting System.

We were concerned that osteonecrosis might be becoming a major HIV-related complication. We hypothesized that, if this were true, additional patients may have developed clinically silent osteonecrosis. Because magnetic resonance imaging (MRI) has been used to study asymptomatic osteonecrosis of the hip in other high-risk populations (32–37), we undertook a prospective MRI-based study to determine the prevalence of and evaluate possible risk factors for asymptomatic osteonecrosis of the hip in a sample of HIV-infected patients.

METHODS

Participant Recruitment and Questionnaire

Between 1 June and 15 December 1999, adults who were enrolled in studies of the treatment or natural history of HIV infection at the NIH Clinical Center or who were receiving health care services at the National Naval Medical Center in Bethesda, Maryland, were invited to participate in an MRI-based screening study of osteonecrosis of the hip. All patients seen in the outpatient clinics of the National Institute of Allergy and Infectious Diseases–National Institute of Health Clinical Center HIV program during the study period were informed of the protocol and encouraged to participate. Because this study focused on asymptomatic patients, we excluded persons with current groin or hip pain.

Because the incidence of osteonecrosis was unknown,
we considered several possible sample sizes (100 to 300 patients) and estimations of the 95% CI for low prevalence rates of asymptomatic osteonecrosis (0.1% to 3.5%). We determined that a sample size of at least 300 HIV-infected participants would be reasonable and attainable. Before undergoing MRI, participants completed a standard questionnaire on joint symptoms; medical history; medication use; and personal habits, including ethanol use, cigarette smoking, and routine exercise regimens. Questions related to medication use made a clear distinction between corticosteroids and other types of steroids, such as androgenic and anabolic steroids. Patients were asked why corticosteroids were prescribed and the route, frequency, and duration of use. The Institutional Review Board of the National Institute of Allergy and Infectious Diseases approved the protocol. All participants gave written informed consent.

Data Collection

We retrieved laboratory and clinical data from patient databases. Laboratory values obtained within 4 months of the MRI date were used in the analyses; for certain variables, we also analyzed the highest or lowest values recorded in a laboratory database that contained data back to 1984.

Physiatrist Evaluation

After approximately 150 patients were scanned and asymptomatic osteonecrosis was detected in 4 patients, we prospectively determined whether subtle physical findings might identify patients with MRI evidence of osteonecrosis of the hip. Patients enrolled after 12 July 1999 were asked (but not required) to be examined by a physiatrist who was unaware of the MRI results. The examination included evaluation of range of motion in the hip, which involved testing in all planes to end range with and without resistance and joint-loading maneuvers; pain was assessed in each test (38).

MRI Scanning

HIV-Infected Participants

Magnetic resonance imaging was performed by using an LX Horizon 1.5-T MRI system (General Electric Medical Systems, Milwaukee, Wisconsin). We modeled the protocol for screening MRI on a previously described method for bilateral screening of the hips for osteonecrosis (37). Coronal T1-weighted spin-echo sequences were done with a repetition time of 400 ms and an echo time of 8 ms (using a $256 \times 192$ matrix). These were followed by coronal fat-suppressed T2-weighted fast spin-echo recovery sequences with a repetition time of 3266 ms, an echo time of 38 ms, and an inversion time of 150 ms ($256 \times 224$ matrix). Other variables used for both screening sequences included three excitations, a $40.0 \times 40.0$–cm field of view, and 5-mm contiguous sections. All MRI scans were initially interpreted by one of the investigators. Positive scans were later intermixed with 35 randomly selected negative scans of HIV-infected participants and were reviewed by a second radiologist, who was unaware of the previous interpretation. Patients with osteonecrosis on the screening MRI underwent dedicated high-resolution MRI of the affected hip or the more abnormal hip.

HIV-Negative Participants

We assumed that asymptomatic osteonecrosis of the hip detectable only by MRI must occur infrequently in healthy adult humans with no known risk factors. To document this, we recruited persons without hip or groin pain who had no known risk factors for osteonecrosis. Exclusion criteria for this comparison group were a history of alcohol abuse, hip or leg fracture, pancreatitis, diabetes mellitus, hypertriglyceridemia (requiring therapy), systemic lupus erythematosus, blood-clotting disorders, or systemic corticosteroid use during the previous year or for greater than 1 month ever (total lifetime use). We recruited these participants from an NIH healthy volunteer database and by posting flyers at the NIH Clinical Center. The participants in the comparison group were approximately matched for age and sex to participants in the screening study HIV-infected patients; the comparison group underwent the MRI screening and consented to participate using the same protocol and procedures that were used in the HIV group.

Hematologic Evaluation

Participants with MRI evidence of osteonecrosis were evaluated for a possible hypercoagulable state by using the following assays: two assays for the presence of a lupus anticoagulant (DRVVT, American Diagnostica, Inc., Greenwich, Connecticut, and Staclot, Diagnostica Stago, Asnieres-Sur-Seine, France); assays for immunoglobulin (Ig)G and IgM anticardiolipin antibodies (Quantite, Innova, San Diego, California); functional assays for protein C, protein S, and antithrombin III levels (Diagnostica Stago; an assay for thrombin–antithrombin complex levels (Dade Behring Marburg, Marburg, Germany); an assay for...
functional plasma activator inhibitor-1 levels (Biopool, Umeå, Sweden); and routine laboratory assays for serum homocysteine and serum lipoprotein(a) levels. These patients were also evaluated for genetic predisposition to hypercoagulability by using restriction enzyme-based genetic tests for factor V Leiden, a prothrombin gene abnormality (G20210A), and for the heat-labile folate reductase (5ⁿ,10ᵗ methylene tetrahydrofolate reductase) gene abnormality, which may lead to hyperhomocystinemia (39–41). For a comparison group, we measured anticardiolipin antibodies, lupus anticoagulant, and protein S levels in a sample of 50 controls with HIV infection who had no evidence of osteonecrosis on MRI. These controls were randomly selected from patients who had been previously scanned as part of the study and who were seen in our clinics for routine visits over a 3-week period (19 November to 9 December 1999).

**Statistical Analysis**

We used the method of Clopper and Pearson (42) to calculate exact CIs for proportions. Associations of osteonecrosis with categorical variables were evaluated by using a two-sided Fisher exact test or, for variables with more than two categories, the Fisher–Freeman–Halton test (43). Associations with continuous variables were evaluated by using a two-sided Wilcoxon rank-sum test with continuity correction. Confidence intervals for relative risks for osteonecrosis were estimated by using the likelihood score method (44). For CIs of odds ratios, we estimated variance according to the method of Robins and colleagues (45). For these calculations, we used the NCSS 2000 software package (Number Cruncher Statistical Systems, Kaysville, Utah) and the StatXact 4 software package (Cytel Software Corp., Cambridge, Massachusetts). We considered \( P \) values less than 0.05 to be statistically significant. All reported \( P \) values are two-tailed and are uncorrected for multiple testing.

**RESULTS**

**Participants**

We performed screening MRI in 339 HIV-infected participants. Twenty-five additional patients asked to participate did not enroll (because of personal reasons \( n = 9 \), claustrophobia \( n = 10 \), or ineligibility for MRI \( n = 6 \)). Of the enrolled patients, 334 were recruited from two clinics sponsored by the National Institutes of Allergy and Infectious Diseases and the Critical Care Medicine department of the NIH Clinical Center. These patients represented approximately 63% of the total population of these clinics. Three and two additional patients were referred from the National Cancer Institute and the National Naval Medical Center, respectively. All patients who received a diagnosis of asymptomatic osteonecrosis were among the 334 patients enrolled from one of the first two sources.

**MRI Findings**

**HIV-Infected Participants**

Fifteen of the 339 participants (4.4% [CI, 2.5% to 7.2%]) had MRI findings consistent with osteonecrosis of the femoral head. Six of these participants had bilateral hip involvement (Figure 1), and 9 had unilateral involvement (Figures 1 and 2). Most of these patients had imaging features similar to those reported previously in other populations—that is, band-shaped or ring-shaped lesions. Three patients with unilateral disease had wedge-shaped lesions in the anteromedial aspect of the femoral head, and another 2 patients with unilateral disease had small subchondral lesions in the anterior superior aspect of the femoral head. All lesions had MRI features characteristic of osteonecrosis: diminished signal on T1-weighted images with a corresponding bright signal on fat-suppressed T2-weighted images. These smaller lesions in the patients with unilateral osteonecrosis were similar to those observed in the less-affected hip of patients with bilateral disease.

When the MRI scans of these 15 patients were intermixed with those of 35 randomly selected HIV-infected participants without osteonecrosis and were reviewed by a second radiologist who was unaware of the initial reading, the agreement between reviewers on whether the scans were positive or negative was 100%. All patients with osteonecrosis on MRI had plain hip radiography. None of these studies was diagnostic for osteonecrosis. Ten of the 15 patients with osteonecrosis reported hip discomfort at some point during the follow-up period (through
May 2002). However, these symptoms were usually mild and transient; no patient has required surgery.

**HIV-Negative Participants**

None of the 118 HIV-negative age- and sex-matched participants had MRI findings consistent with osteonecrosis ($P = 0.015$ for comparison with HIV-infected participants).

**Physical Examination Findings**

One hundred sixty-eight of 191 patients who enrolled after 12 July 1999 were prospectively examined by a physiatrist, including 10 of 11 patients in whom osteonecrosis was subsequently detected by MRI. No single test or combination of tests was predictive of osteonecrosis. Although 14 of 16 hips with evidence of osteonecrosis had one or more abnormal findings on physical examination and 11 of
Table 1. Clinical and Laboratory Characteristics of 339 Asymptomatic HIV-Infected Patients Evaluated for Osteonecrosis by Magnetic Resonance Imaging*

| Characteristic                              | Patients with Osteonecrosis (n = 15) | Patients without Osteonecrosis (n = 324) | P Value |
|---------------------------------------------|--------------------------------------|-------------------------------------------|---------|
| Age, y                                      | 44.4 ± 7.8                           | 41.9 ± 7.6                                | >0.2    |
| Male sex, n (%)                             | 14 (93)                              | 297 (92)                                  | >0.2    |
| Race/ethnicity, n (%)                       |                                      |                                           | >0.2    |
| Non-Hispanic white                          | 12 (80)                              | 261 (81)                                  |         |
| Non-Hispanic black                          | 2 (13)                               | 43 (13)                                   |         |
| Hispanic                                    | 1 (7)                                | 16 (5)                                    |         |
| Other                                       | 0                                    | 4 (1)                                     |         |
| Risk factors for HIV infection, n (%)†      |                                      |                                           | >0.2    |
| Homosexual                                  | 14 (93)                              | 279 (86)                                  |         |
| Heterosexual                                | 1 (7)                                | 39 (12)                                   |         |
| IV drug use, other                          | 0                                    | 6 (2)                                     |         |
| Time since HIV diagnosis, mo                | 123 ± 43                             | 104 ± 48                                  | >0.2    |
| CD4+ cell count, ×10^9 cells/L             | 0.574 ± 0.182                        | 0.672 ± 0.373                             | >0.2    |
| HIV viral load, log copies/mL‡             | 3.1 ± 1.3                            | 2.5 ± 1.1                                 | 0.05    |
| Closest to MRI                              | 4.8 ± 1.1                            | 4.6 ± 1.0                                 | >0.2    |
| Lowest recorded                             | 0.233 ± 0.120                        | 0.281 ± 0.164                             | >0.2    |
| Closest to MRI                              | 5.85 ± 10.56 (518 ± 935)             | 3.03 ± 3.33 (268 ± 295)                   | 0.15    |
| Highest recorded                            | 12.93 ± 14.35 (1145 ± 1271)          | 6.50 ± 6.39 (576 ± 566)                   | 0.07    |
| Serum triglyceride level, mmol/L (mg/dL)    |                                      |                                           |         |
| Closest to MRI                              | 7.01 ± 1.86 (271 ± 72)               | 5.30 ± 1.86 (265 ± 72)                    | >0.2    |
| Highest recorded                            | 7.53 ± 2.66 (291 ± 103)              | 6.52 ± 2.12 (252 ± 82)                    | 0.08    |
| Hematocrit                                  |                                      |                                           |         |
| Closest to MRI                              | 0.42 ± 0.055                         | 0.43 ± 0.043                              | >0.2    |
| Highest recorded                            | 0.47 ± 0.044                         | 0.47 ± 0.037                              | >0.2    |
| Platelet count, ×10^12 cells/L             |                                      |                                           |         |
| Closest to MRI                              | 233 ± 43                             | 219 ± 63                                  | >0.2    |
| Highest recorded                            | 305 ± 84                             | 262 ± 85                                  | 0.04    |

* Values expressed with the plus/minus sign are means ± SD. Because of rounding, percentages may not equal 100. Data were missing on some patients without osteonecrosis. IV = intravenous; MRI = magnetic resonance imaging.
† Three homosexual men and 2 women also had a history of IV drug use.
‡ For viral load levels below the level of detection of the assay—that is, <500 or <50 copies/mm³—values of 499 or 49, respectively, were used in the calculations.
§ Protease inhibitor use includes all patients who ever used these agents; duration represents total duration of therapy.

16 had abnormal range of motion; these proportions were not significantly different than those found when the hips of participants with no abnormality on MRI were examined (data not shown).

Comparison of HIV-Infected Patients with and without Osteonecrosis

HIV-infected patients with osteonecrosis did not differ significantly from patients without osteonecrosis in age, sex, or ethnicity/race (Table 1). The two groups were also similar for variables related to the underlying HIV infection—risk group, time since diagnosis, CD4+ T-cell count, and pattern of antiretroviral use. However, the mean HIV-1 viral load recorded closest to the date of the MRI and the highest recorded platelet count were significantly higher in the patients with osteonecrosis.

Evaluation of Risk Factors

An analysis of possible risk factors showed an increased relative risk for osteonecrosis in patients with any lifetime use of systemic corticosteroids, lipid-lowering agents, or testosterone and in patients with a history of weightlifting or bodybuilding (Table 2).

Fourteen of 15 patients with osteonecrosis (93%) had anticardiolipin antibodies. In 7 patients with osteonecrosis, anticardiolipin antibody levels were greater than 23 IgG phospholipid units (a level associated with predisposition to thrombosis [46], compared with 5 of 50 HIV-infected patients without osteonecrosis (10%). The relative risk for osteonecrosis in patients with levels greater than 23 IgG phospholipid units was 3.9 (CI, 1.7 to 8.3). None of the 15 patients with osteonecrosis nor any of the 50 HIV-infected patients without osteonecrosis showed evidence of lupus anticoagulation. Other tests for hypercoagulability showed no increase in relative risk for osteonecrosis.

Discussion

We documented an extraordinarily and unexpectedly high occurrence of osteonecrosis of the hip in HIV-infected patients; 15 of 339 participants studied (4.4% [CI, 2.5% to 7.2%]) had characteristic lesions of osteonecrosis on MRI. No abnormalities consistent with osteonecrosis were seen in age- and sex- matched controls without HIV infection, who were selected specifically because they had...
no known risk factors for osteonecrosis. Therefore, these findings are not incidental but are somehow attributable to HIV infection or therapy. Case reports of osteonecrosis of the hip in HIV-infected persons at other centers (7–31) support our observations. Thus, osteonecrosis appears to be another complication of HIV disease or related therapies that could cause considerable morbidity and require substantial resources for optimal management.

We focused on asymptomatic patients in an attempt to identify the earliest stage of disease. Magnetic resonance imaging has become the preferred technique for the diagnosis of osteonecrosis, particularly early and asymptomatic lesions that may not be detected on routine radiographic studies (47–50). Our study supports this notion because no participant with osteonecrosis showed abnormality on plain radiographs; thus, these radiographs are not useful in early detection of osteonecrosis. Defining the natural history of asymptomatic osteonecrosis in HIV-infected patients is a critical next step. At present, recommending routine screening for occult lesions of osteonecrosis would be premature. Timely MRI evaluation of patients with persistent symptoms in the groin or hip would seem to be a more appropriate approach.

Because a less costly screening tool than MRI would be beneficial, we prospectively evaluated the diagnostic utility of a targeted physical examination by an experienced physiatrist in a subset of patients. Although this approach did not reliably identify patients with osteonecrosis, only two patients had no abnormality on examination of the hip. Further evaluation of the sensitivity and specificity of these tests alone and in combination is needed to evaluate the utility of the physical examination as an adjunctive screening tool.

Although protease inhibitors have been implicated in osteonecrosis (12, 15, 23, 28), we found no association between osteonecrosis and use or duration of protease inhibitor therapy—possibly because these drugs are so widely used (in >90% of HIV-infected patients with or without osteonecrosis). Thus, our results cannot be extrapolated to patients who are not receiving protease inhibitor therapy. Osteonecrosis was reported in HIV-infected patients before protease inhibitors became available (9, 17). Although serum lipid levels in our study were associated only marginally with osteonecrosis, a history of use of lipid-lowering agents, which is probably a surrogate marker for more severe hyperlipidemia, was strongly correlated with osteonecrosis. Evidence of this association supports the hypothesis that protease inhibitors play a role in the development of osteonecrosis through a tendency to cause hyperlipidemia (12, 15, 31). Alternatively, protease inhibitors may inhibit the metabolism of drugs that are metabolized by the cytochrome p450 system, such as corticosteroids (51).

Only one patient in our study had a history of prolonged exposure (approximately 2 years) to systemic corticosteroids. In the remainder of patients, the estimated total exposure ranged from several days to several weeks. Although prolonged corticosteroid use is a well-recognized risk factor for osteonecrosis, this complication has been reported among patients who have received relatively short courses (52). Factors related to the underlying condition for which corticosteroids are used appear to modify the risk for osteonecrosis (53, 54). For example, when corticosteroids are used to treat patients with inflammatory arthritis or asthma, the risk appears to be small (55); the risk from corticosteroids is substantially greater in patients who have renal transplantation (56). Our data suggest that HIV-infected patients are currently at increased risk for osteonecrosis and that even short courses of corticosteroid therapy might further increase that risk substantially. The reasons for this are unclear. Health care providers and patients should weigh the potential benefit of systemic corticosteroid use in HIV-infected patients against the possibility

### Table 2. Associations between Osteonecrosis and Health-Related Characteristics in HIV-Infected Persons

| Characteristic | Proportion of Patients with Osteonecrosis, n/n (%) | Relative Risk (95% CI) |
|---------------|--------------------------------------------------|------------------------|
| **Medical history*** | | |
| AIDS-defining opportunistic infection | 5/56 (8.9) | 10/283 (3.5) | 2.5 (0.9–6.7) |
| Malignant disease | 10/215 (4.7) | 5/115 (4.3) | 1.1 (0.4–2.9) |
| **Fat redistribution** | | |
| (any)† | 7/97 (7.2) | 8/218 (3.7) | 2.0 (0.8–5.1) |
| **Pancreatitis** | 0/11 (0) | 15/321 (4.7) | 0.0 (0–5.8) |
| **Low serum testosterone level** | 0/10 (0) | 15/329 (4.6) | 0.0 (0–6.4) |
| **Alcohol abuse** | 2/32 (6.3) | 13/305 (4.3) | 1.5 (0.4–5.3) |
| **History of medication use‡** | | |
| Oral or parenteral corticosteroids | 11/143 (7.7) | 4/196 (2.0) | 3.8 (1.3–11.0) |
| Lipid-lowering agents | 7/53 (13.2) | 8/285 (2.8) | 4.7 (1.8–11.9) |
| Testosterone | 10/121 (8.3) | 4/190 (2.1) | 3.9 (1.3–11.6) |
| Megestrol acetate | 1/21 (4.8) | 14/318 (4.4) | 1.1 (0.2–5.6) |
| Interleukin-2 | 1/21 (4.8) | 14/318 (4.4) | 1.1 (0.2–5.6) |
| **Routine exercise regimen§** | | |
| Lifts weights or uses bodybuilding apparatus | 11/149 (7.4) | 4/181 (2.2) | 3.3 (1.1–9.8) |
| Uses treadmill or similar device | 6/94 (6.4) | 9/236 (3.8) | 1.7 (0.6–4.4) |
| Jogs, runs, walks | 5/135 (3.7) | 10/195 (5.1) | 0.7 (0.3–2.0) |
| Rides bicycle | 2/46 (4.3) | 13/284 (4.6) | 0.9 (0.2–3.5) |
| Personal habits | 9/246 (3.7) | 6/84 (7.1) | 0.5 (0.2–1.4) |
| Consumes alcohol | 2/99 (2.0) | 13/231 (5.6) | 0.4 (0.1–1.4) |

* Data on opportunistic infections and on alcohol abuse were collected from patient records. Data on gout, pancreatitis, and hypertension were collected from patient records and questionnaires. Women were excluded from testosterone analysis.
† Fat redistribution is based on participant questionnaire responses about whether they had noted any of the following: loss of fat in the face; loss of fat in the arms, extremities, or buttocks; collection of fat in the abdomen; collection of fat in the upper back (“buffalo hump”). For all noted elements, the participant was asked whether the element was mild, moderate, or severe.
‡ Includes all patients who had ever used these agents. Data are based on patient records and questionnaires completed before undergoing screening magnetic resonance imaging. Women were excluded from the analyses of testosterone use.
§ Data on exercise regimen and personal habits are based on the questionnaires completed before screening magnetic resonance imaging.

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that the drugs may increase the risk for osteonecrosis to an even greater degree than that of patients without HIV infection (57).

We identified additional potential risk factors associated with osteonecrosis in HIV-infected patients, although we could not determine whether these associations are incident or causal. Because few patients had osteonecrosis, we did not perform a multivariate analysis of risk factors. Abnormalities of coagulation, including those associated with the presence of anticardiolipin antibodies, have been associated with osteonecrosis in other settings and thus may play a role in HIV-infected patients (58).

We identified other factors that have not typically been associated with osteonecrosis. However, it is plausible that bodybuilding may increase intra-articular forces that could lead to injury and that testosterone deficiency could contribute through adverse effects on bone metabolism. Although supraphysiologic levels of testosterone have not been reported to be associated with osteonecrosis in other settings, at least four of the participants with osteonecrosis who were receiving testosterone did not have testosterone deficiency, suggesting that testosterone replacement may increase risk.

Several additional limitations of our study deserve mention. Because women and ethnic and racial minority groups were underrepresented in our sample (a result of the clinic population from which participants were recruited), the incidence of osteonecrosis and potential contributing risk factors could conceivably differ in these populations. Although our patients were self-referred for this study, we believe that the potential for selection bias was low because all patients seen in the two primary recruitment sites during the study period were allowed to participate, and 63% enrolled. Moreover, patients referred for the study with any hip, buttock, or groin symptoms were offered MRI screening outside the study setting. Furthermore, alcohol use may have been underreported because data for this variable came solely from the questionnaire responses.

If osteonecrosis ultimately requiring hip replacement occurs in 1% to 2% of HIV-infected patients per year and if a smaller proportion of patients have symptoms in other bones (as we have already seen), prospective studies of management strategies to minimize the occurrence of this complication are urgently needed. If protease inhibitors are important causative factors or cofactors, an antiretroviral therapy strategy that minimizes protease drug exposure will become even more attractive. If brief exposure to corticosteroids is an important factor or if long-term exposure to lipid-lowering agents is significant, then strategies to treat immune reactivation syndromes or long-term cardiovascular risk, respectively, may need to be reassessed. Long-term surveillance of HIV-infected patients treated with new drugs and new drug combinations remains essential to the recognition of unexpected complications, such as osteonecrosis, and the development of management programs to minimize the risks for disabling or fatal complications.

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References
1. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338:853-60. [PMID: 9516219]
2. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet. 2000;356:1423-30. [PMID: 11052597]
3. Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). N Engl J Med. 1992;326:1473-9. [PMID: 1574093]
4. Mirzai R, Chang C, Greenspan A, Gershwin ME. Avascular necrosis. Compr Ther. 1998;24:251-5. [PMID: 9626482]
5. Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head. J Bone Joint Surg Am. 1995;77:459-74. [PMID: 7890797]
6. Gooßen BP, Lacey H, Thurairajasingam S, Brown JD. Avascular necrosis of the hip in a man with HIV infection. Genitourin Med. 1996;66:451-2. [PMID: 2265845]
7. Manzaneque González L, Mayoral Martín L, Jiménez Ocaña C, Corzo Delgado JE, Sánchez-Matas Rodríguez P, Grillo Reina A. [Bilateral avascular necrosis of the femur head in an HIV-positive male]. An Med Interna. 1994;11:601-3. [PMID: 7734669]
8. Cone LA, Byrd RG, Hirschberg JM, Poets B. The cardiolipin syndrome in HIV+ patients [Abstract]. Presented at 3rd Conference on Retroviruses and Opportunistic Infections, 28 January–1 February 1996, Washington, D.C. Abstract no. 126. Accessed at http://gateway.nlm.nih.gov on 23 May 2002.
9. Chevalier X, Larget-Piet B, Hernigou P, Gherardi R. Avascular necrosis of the femoral head in HIV-infected patients. J Bone Joint Surg Br. 1993;75:160. [PMID: 8421018]
10. Belmonte MA, García-Portales R, Domènech I, Fernández-Nebro A, Camps MT, De Ramón E. Avascular necrosis of bone in human immunodeficiency virus infection and antiphospholipid antibodies. J Rheumatol. 1993;20:1425-8. [PMID: 8230033]
11. De Truchis P, Saillour M, Avisé M, Grillo Reina A, Mancini L, Pignatelli M, et al. Avascular necrosis of bone in HIV-infected patients with antiphospholipid antibodies [Abstract]. Presented at 3rd International Conference on AIDS, Vancouver, British Columbia, Canada, 7–12 July 1996. Abstract no. Mo.B. 1298. Accessed at http://gateway.nlm.nih.gov on 23 May 2002.
12. Timponi J, Fuhme D, Nascone J, Evans B, Kumar P. Avascular necrosis in HIV+ patients: a potential link to protease inhibitors [Abstract]. Presented at 6th Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, 31 January–4 February 1999. Abstract no. 680. Accessed at http://gateway.nlm.nih.gov on 23 May 2002.
13. Koeger AG, Banneville B, Gerster J-C, de Bandt M, Pollack Y, Fritz P, et al. Avascular necrosis in HIV-infected patients: 10 cases [Abstract]. Arthritis
Osteonecrosis in HIV Infection

Rheum. 1995;38(Suppl 9):S199.

14. Koeger AC. Osteonecrosis and human immunodeficiency virus infection [Letter]. J Rheumatol. 1995;22:752-3. [PMID: 10090198]

15. Meyer D, Behrens G, Schmidt RE, Stoll M. Osteonecrosis of the femoral head in patients receiving HIV protease inhibitors [Letter]. AIDS. 1999;13:1147-8. [PMID: 10397552]

16. Martín-Crespo R, Escorihuela A, Sotole J, Gurbindo MD, Sampeyalo I, Luque MR, et al. Hip disease in AIDS children [Abstract]. Presented at 8th International AIDS Conference, Amsterdam, the Netherlands, 19–24 July 1992. Abstract no. PuB 7340. Accessed at http://gateway.nlm.nih.gov/ on 23 May 2002.

17. Gerster JC, Campus JP, Chave JP, Koeger AC, Rapportor G. Multiple site avascular necrosis in HIV infected patients. J Rheumatol. 1991;18:300-2. [PMID: 2032327]

18. Solomon G, Branco L, Winchester R. An approach to the human immunodeficiency virus-positive patient with a spondyloarthropathic disease. Rheum Dis Clin North Am. 1991;17:43-58. [PMID: 2041888]

19. Stovall D Jr, Young TR. Avascular necrosis of the medial femoral condyle in HIV-infected patients. Am J Orthop. 1995;24:71-3. [PMID: 7773659]

20. Scribner AN, Troia-Cancio PV, Cox BA, Marcantoni D, Hamid F, Keiser P, et al. Osteonecrosis in HIV: a case-control study. J Acquir Immune Defic Syndr. 2000;25:19-25. [PMID: 11064500]

21. Blangy H, Louelle D, Charwy-Valckenaire I, Christian B, May T, Gillet P. Osteonecrosis of the femoral head in HIV-1 patients: four additional cases [Letter]. J Rheumatol. 1995;22:214-5. [PMID: 7763570]

22. Roulière L, Viard JP. Osteonecrosis of the hip, lipodystrophy and antiretroviral treatment [Letter]. AIDS. 2000;14:2056. [PMID: 10997415]

23. Sighinolfi L, Carradori S, Ghinelli F. Osteonecrosis of the femoral head: a side effect of highly active antiretroviral therapy (HAART) in HIV patients? [Letter] Infection. 2000;28:254-5. [PMID: 10961537]

24. Blacksin MF, Kloser PC, Simon J. Avascular necrosis of bone in human immunodeficiency virus infected patients. Clin Imaging. 1999;23:314-8. [PMID: 10665350]

25. Johns DG, Gill MJ. Avascular necrosis in HIV infection [Letter]. AIDS. 1999;13:1997-8. [PMID: 10156372]

26. Laugier J, Palmer J, Rosón N, Fernández A, Camisas A. Osteonecrosis of the knee in an HIV-infected patient. AJR Am J Roentgenol. 1998;171:987-8. [PMID: 9762981]

27. Olivé A, Queralt C, Sirera G, Centelles M, Force L. Osteonecrosis and HIV infection: 4 more cases [Letter]. J Rheumatol. 1998;25:1243-4. [PMID: 9632097]

28. Monier P, McKown K, Bronze MS. Osteonecrosis complicating highly active antiretroviral therapy in patients infected with human immunodeficiency virus. Clin Infect Dis. 2000;31:1488-92. [PMID: 11096017]

29. Roudie J, Dobro JS, Solomon G. Osteonecrosis and human immunodeficiency virus infection. J Rheumatol. 1997;24:601-4. [PMID: 9058674]

30. Koller E, Mann M, Malozowski S, Bacsanyi J, Gibert C. Aseptic necrosis in HIV seropositive patients: a possible etiologic role for megestrol acetate. AIDS. 1999;13:80:243-50. [PMID: 9400059]

31. Colwell CW Jr, Robinson CA, Stevenson DD, Vint VC, Morris BA. Aseptic necrosis of the femoral head: MR imaging for prognosis in 31 cases with at least 2 years of follow-up. Radiology. 1993;187:199-204. [PMID: 8451413]

32. Sugano N, Ohzono K, Masuhara K, Takaoka K, Ono K. Prognostication of osteonecrosis of the femoral head in patients with systemic lupus erythematosus by magnetic resonance imaging. Clin Orthop. 1994;1:109-9. [PMID: 8050228]

33. Salamont M, Shimizu K, Iida S, Akita T, Moriya H, Nawata Y. Osteonecrosis of the femoral head: a prospective study with MRI. J Bone Joint Surg Br. 1997;79:213-9. [PMID: 9119845]

34. Tervonen O, Mueller DM, Matteson EL, Velosa JA, Ginsburg WW, Ehman RL. Clinically occult avascular necrosis of the hip: prevalence in an asymptomatic population at risk. Radiology. 1992;182:845-7. [PMID: 1535906]

35. Young J, Olsen NK, Press JM. Musculoskeletal disorders of the lower limbs. In: Braddock RL, ed. Physical Medicine and Rehabilitation. Philadelphia: WB Saunders; 1996:783-812.

36. Ridker PM, Hennekens CH, Lindpaintner K, Stampler MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med. 1995;332:912-7. [PMID: 8787648]

37. Blangy H, Loeuille D, Chary-Valckenaere I, Christian B, May T, Gillet P. Osteonecrosis of the femoral head in HIV-1 patients: four additional cases [Letter]. J Rheumatol. 1995;79:213-9. [PMID: 9119845]

38. Fordyce MJ, Solomon L. Distinguishing transient osteoporosis from avascular necrosis of the hip. J Bone Joint Surg Am. 1995;77:616-24. [PMID: 7713981]

39. Vande Berg BC, Malghem J, Lescovet FE, Noel H, Maldague B. MR imaging of bone infarction and epiphyseal osteonecrosis. J Bone Jt Radiol. 1997;77:243-50. [PMID: 9400059]

40. Sugano N, Kubo T, Takaoka K, Ohzono K, Hotokebuchi T, Matsumoto T, et al. Diagnostic criteria for non-traumatic osteonecrosis of the femoral head. A multicentre study. J Bone Joint Surg Br. 1999;81:590-5. [PMID: 10463726]

41. Varis T, Kivistö KT, Backman JT, Neuvonen PJ. The cytochrome P450 3A4 inhibitor itraconazole markedly increases the plasma concentrations of dexamethasone and enhances its adrenal-suppressant effect. Clin Pharmacol Ther. 2000;68:487-94. [PMID: 11103751]

42. Chang CC, Greenspan A, Gershwin ME. Osteonecrosis: current perspectives on pathogenesis and treatment. Semin Arthritis Rheum. 1999;29:47-69. [PMID: 8255665]

43. Mirzai R, Chang C, Greenspan A, Gershwin ME. The pathogenesis of osteonecrosis and the relationships to corticosteroids. J Arthrum. 1999;36:77-95. [PMID: 10077138]

44. Mont MA, Glueck CJ, Pacheco IH, Wang P, Hungerford DS, Petri M. Risk factors for osteonecrosis in systemic lupus erythematosus. J Rheumatol. 1997;24:654-62. [PMID: 9104971]

45. Colwell CW Jr, Robinson CA, Stevenson DD, Vint VC, Morris BA. Osteonecrosis of the femoral head in patients with inflammatory arthritis or asthma receiving corticosteroid therapy. Orthopedics. 1996;19:941-6. [PMID: 8936529]

46. Patton PR, Pfaff WW. Aseptic bone necrosis after renal transplantation. Surgery. 1988;103:63-8. [PMID: 3276031]

47. Gallant JE. When to consider corticosteroid therapy for HIV-infected patients. The AIDS Reader. 1999;6:602-8.

48. Glueck CJ, Freiberg R, Tracy T, Sroop D, Wang P. Thrombophila and hypofibrinolysis: pathophysiology of osteonecrosis. Clin Orthop. 1997;43-56. [PMID: 9005895]
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