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Original article

Decreased serum bone specific alkaline phosphatase and increased urinary N-terminal telopeptide of type I collagen as prognostic markers for bone mineral density loss in HIV patients on cART

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ABSTRACT

Objectives: Bone mineral density (BMD) loss is a major chronic complication in HIV patients. We performed a prospective study to determine the time course of BMD changes and to find prognostic factors of BMD loss in HIV patients on combination antiretroviral therapy (cART).

Patients and methods: Subjects were 54 male Japanese HIV patients who had been on cART ≥1 year with no therapeutic agents for osteoporosis. Patients were observed for ≥1 year (median 3.1 years) and underwent annual BMD analyses using dual energy X-ray absorptiometry. Changes in BMD at lumbar spine and femoral neck were calculated for each person-year of all the patients. Clinical factors were also collected simultaneously with BMD examinations to determine prognostic factors for BMD loss.

Results: In total, 173 person-years in 54 patients were observed. One third (19, 35.2%) and slightly over half (30, 55.6%) patients showed BMD decreases at lumbar spine and femoral neck, respectively. However, the median BMD changes at lumbar spine and femoral neck were 0.0% and −0.52% per year, respectively. Monovariant and mixed model analyses determined that decreased serum bone specific alkaline phosphatase (BAP, $p = 0.0047$) and increased urinary N-terminal telopeptide (uNTx, $p = 0.0011$) were prognostic factors for BMD loss at lumbar spine and femoral neck, respectively.

Conclusions: BMD at both lumbar spine and femoral neck changed little on average in HIV patients on cART. Decreased serum BAP or increased uNTx may be helpful to predict progressive BMD loss in the following year and to select patients for BMD follow-up or initiation of anti-osteoporosis treatment.

The main point of the article

BMD changed little on average among HIV patient continuing cART for more than 1 year. Decreased serum bone specific alkaline phosphatase and increased N-terminal telopeptide of type I collagen were identified as prognostic markers of BMD decreases in the following year.

1. Introduction

The mortality of individuals with HIV dramatically improved with the introduction of combination antiretroviral therapy (cART) in the mid-1990s. As a result, the impact of opportunistic infections has been replaced by the impact of chronic complications, including loss of bone mineral density (BMD) and fragility fractures [1–3]. Cross-sectional cohort studies have described a significantly higher prevalence of BMD loss in HIV infected patients in numerous countries [4–8]. As we reported previously, this is a problem not only in western countries; there are also considerable rates of osteopenia and osteoporosis in Japan [6]. Furthermore, Brown and colleagues revealed that the prevalence of osteoporosis in HIV infected patients was 15% and this value represented a 3.7-fold increase compared with age-matched HIV uninfected controls [2].

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These conditions are often associated with a decrease in physical function and quality of life [9].

The reasons of this are thought to be multifactorial; including the classical causes of osteoporosis in the general population, such as low body mass index (BMI), current glucocorticoid treatment, smoking, and excessive alcohol intake. However, other causes should also be considered in patients with HIV, such as the effects of HIV proteins and antiretroviral agents as well as chronic inflammation [10–12]. HIV itself is suspected to have an influence on BMD loss and it may occur in very early stages of HIV infection [4]. In addition, cART initiation is strongly associated with BMD loss; the most bone loss occurs in the first 6–12 months after cART initiation in most patients [13,14].

However, it remains to be determined how BMD changes in the long term in HIV patients after the first 12 months from cART initiation. A matter of utmost concern for clinicians is "who is likely to lose BMD and what are the prognostic factor of decreasing BMD in the near future?" To clarify this problem, we performed a prospective study to determine the time course of BMD changes among patients with HIV receiving cART for more than one year. In addition, we tried to identify prognostic markers of BMD loss among these patients.

2. Patients and methods

2.1. Study population

Subjects were male Japanese patients with HIV who visited Teikyo University Hospital (Tokyo, Japan) and who had been receiving cART for 1 year or longer and agreed to join the study. Patients who were prescribed any therapeutic agents for osteoporosis were not enrolled in the study and patients who experienced pathological fractures of spines or femoral necks during the observation period were excluded from the study since these fractures may cause false increase of BMD by DXA scanning. This prospective study was performed in accordance with the Helsinki Declaration of the World Medical Association and was approved by the ethical committee of Teikyo University School of Medicine. All patients gave written informed consent and information was kept anonymous as far as possible.

2.2. BMD analyses

Patients were enrolled in the study from March 2010 to September 2014 and observed until September 2015. They underwent BMD analyses annually including at the start of the observation period. Patients' BMDs were measured with the same dual energy X-ray absorptiometry (DXA) scanner (Discovery SI, Hologic Inc, Bedford, MA, USA). They were also monitored for the presence of pathologic fractures by X-ray examination concomitantly with each DXA scanning. All the patients underwent analyses of both lumbar spine and femoral neck. BMD data from all points were used to calculate T-scores, which were defined as the comparison with young normal reference values expressed as SD units. Osteopenia was defined as a T-score of between −1 and −2.5 SD, and osteoporosis was defined as ≤ -2.5 based on the World Health Organization classification [15].

Annual percentage changes in BMD at lumbar spine and femoral neck were separately calculated for each person-year of all the patients and these were named dif.lum% and dif.fem%, respectively. To determine the prognostic factors of BMD loss, dif.lum% and dif.fem% were calculated by using BMD at each time point and BMD at the following year.

2.3. Clinical backgrounds

Collected clinical factors included age, height, body weight, smoking status (measured by pack year), use of corticosteroids, CD4 cell counts at study entry, duration of cART, use of nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI), serum creatinine, bone specific alkaline phosphatase (BAP) levels, estimated glomerular filtration rate (eGFR), serum N-terminal telopeptide of type I collagen (NTx) and urinary NTx levels corrected for creatinine (uNTx), parathormone and serum calcium corrected for albumin, serum phosphate, urinary calcium and urinary phosphate [16]. Patients' blood and urine were taken during their routine visit to the hospital in the morning. The eGFR for Japanese male patients was calculated as $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ (mL/min per 1.73 m^2) [17].

2.4. Statistical analysis

Subgroup analyses were performed by *t*-test with Welch's modification for comparisons of patients with smoking history (more than one pack-year) versus those without smoking history, corticosteroid recipients (more than 0.5 g of prednisolone in one's lifetime) versus non-recipients, PI recipients versus non-PI recipients and the tenofovir/emtricitabine (TDF/FTC) recipients versus non-TDF/FTC recipients. Correlation coefficients for clinical factors at the beginning of person-year observation were analyzed for both dif.lum% and dif.fem%. To determine prognostic variables for dif.lum% or dif.fem%, variables that exhibited a correlation or tendency of correlation with dif.lum% or dif.fem% were used in multivariable analyses following the method of mixed model analyses. Mixed model analysis is a statistical model contained both fixed effect and random effect particularly useful in settings where repeated measurements are made on the same statistical units for longitudinal study. In our study, patient ID and clinical factors were employed as the random effect variable and fixed effect variables, respectively. All analyses were performed using JMP Pro version 12.0.1 (SAS Institute Inc., Cary, NC, USA) and Graphpad Prism version 6.0g (Graphpad Software, Inc., La Jolla, CA, USA).

3. Results

Baseline characteristics of participants are shown in Table 1. The overall number of the patients was 60. From 60 patients, one patient was excluded for pathological fracture of left femoral neck, and four could not arrange their follow-up BMD measurements schedules and one moved to other hospital. One patient experienced traumatic fracture of right humerus, however, he was included in the study by following the criteria. The final number of patients in the study was 54.

The median observation period was 3.1 years (range 1.0–5.2 years); 173 person-years were observed in total. All the patients continued cART for at least 1 year and the median duration of cART at study entry was 2.2 years (range 1.0–15.0 years). Therefore, HIV viral load remained undetectable in most patients and the median CD4 cell count was 514/μL. In total, 45 (83.3%) patients were prescribed PI therapy, 21 patients (38.9%) took abacavir (ABC)/lamivudine (3TC) and 30 (55.6%) took TDF/FTC.

The distributions of T-scores at lumbar spine and femoral neck, and the smaller T-score of the two at the first examination are plotted in Fig. 1a. Among 54 patients, 28 (51.9%) and 2 (3.7%) were diagnosed with osteopenia and osteoporosis, respectively, at lumbar spine and 28 (51.9%) and 4 (7.4%) were diagnosed with osteopenia and osteoporosis, respectively, at femoral neck. By choosing the smaller T-score of the two, approximately 70% of the patients were diagnosed with either osteopenia (32, 59.3%) or osteoporosis (6, 11.1%). In Fig. 1b, the distributions of T-scores at lumbar spine and femoral neck and smaller T-score of the two at the latest BMD examination of each patient are shown. The number of patients diagnosed with osteopenia (33, 61.1%) or