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Original Article

Protease inhibitor-associated bone mineral density loss is related to hypothyroidism and related bone turnover acceleration

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ABSTRACT

Background: Clinical and experiments evidence indicate that protease inhibitors (PI) can cause bone mineral density (BMD) loss. However, the mechanism of such loss remains obscure.
Methods: This single-center, cross-sectional study included 184 HIV-infected patients treated with PI who underwent dual-energy X-ray absorptiometry scan. Serum phosphorus, percentage of tubular reabsorption of phosphate (%TRP), thyroid and parathyroid function (iPTH), vitamin D, osteocalcin (OC), urinary deoxypyridinoline (DPD), and urinary cross-linked N-telopeptide of type I collagen (u-NTx) were measured.
Results: The rate of hypothyroidism in PI-users [32/117 (27%)] was double that in non-PI users [8/67 (12%), $p = 0.016$] and was significantly associated with PI use in multivariate analysis [odds ratio (OR) 11.37, 95% confidence interval (CI) 1.358–95.17, $p = 0.025$]. Spine BMD was significantly lower in hypothyroid patients than euthyroid, for both total population (−1.37 vs. −1.00, p = 0.041) and PI users (−1.56 vs. −1.13, p = 0.029). Multivariate regression analysis identified inverse correlation between hypothyroidism and spine BMD [estimate −0.437, 95% CI -0.858 to −0.024, $p = 0.042$]. OC, DPD and u-NTx were significantly higher in PI users than in non-PI users ($p = 0.01$, 0.05, and 0.01, respectively).
Conclusions: PI use is associated with hypothyroidism as well as bone turnover acceleration, which worsens PI-associated BMD loss. In PI-treated patients, thyroid function tests are warranted to prevent further progression of PI-associated BMD loss.

1. Introduction

For HIV-infected patients, loss of bone mineral density (BMD) is an important age-related complication, and the prevalence of osteoporosis among HIV-infected patients is reported to be three times that in HIV-negative population [1]. Although the etiology of low BMD in HIV-infected patients is multifactorial, including chronic HIV infection [2,3] and tenofovir disoproxil fumarate (TDF) [4,5], clinical evidence indicates that protease inhibitor (PI) is one of the most important risk factors of BMD loss [4,6–8]. However, the mechanism of PI-associated BMD loss is not fully elucidated, and thus, there are currently no reliable biochemical markers for PI-associated BMD loss. The present study was designed to evaluate the association among PI use, BMD loss, and biochemical markers of bone metabolism.

2. Patients and methods

2.1. Setting and participants

Patients of this study were the same who participated in our recent cross-sectional study at the AIDS Clinical Center (ACC), National Center for Global Health and Medicine (NCGM), which included HIV-infected patients registered at the NCGM between February 2012 and June 2013 [8]. We excluded patients who had been on treatment for osteoporosis, current users of corticosteroids, and those with history of bone fractures at spine or femoral neck. Thus, 184 Japanese HIV-infected men were enrolled in this study, who were either on PI users (n = 117) or non-users (n = 67).

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The study was approved by the Human Research Ethics Committee of National Center for Global Health and Medicine (NCGM-G-001261-00). All patients included in this study provided written informed consent for their clinical and laboratory data to be used and published for research purposes. The study was conducted according to the principles expressed in the Declaration of Helsinki.

2.2. Data collection

BMD was assessed using dual X-ray absorptiometry (DXA: QDR-4500 W, Hologic Inc., Bedford, MA) at the lumbar spine and femoral neck. Age, body mass index (BMI), smoking habit, hemophilia, and history of AIDS-defined illness, were obtained by interview or medical records. The estimated glomerular filtration rate (eGFR) was calculated using the modified Modification of Diet in Renal Disease (MDRD) equation for Japanese populations [9]. On the same day of DXA scan, serum phosphorus (s-IP), the percentage of tubular reabsorption of phosphate (%TRP), low density lipoprotein-cholesterol (LDL-C), thyroid-stimulating hormone (TSH), serum free triiodothyronine (FT3), serum free thyroxine (FT4), intact parathyroid function (iPTH), 25 (OH)-Vitamin D, bone-specific alkaline phosphatase (BAP), osteocalcin (OC), urinary deoxypyridinoline (DPD) and urinary cross-linked N-telopeptide of type I collagen (u-NTx) were measured.

TSH, FT3, and FT4 serum levels were measured by electrochemiluminescence immunoassay kit (Roche Diagnostics, Indianapolis, IN). The normal ranges of TSH, FT3, and FT4 were set according to the instructions provided by the manufacturer. Euthyroidism was defined as TSH level of >0.5 to <5 mIU/L with FT4 level of >0.8 to <1.7 ng/dL. Overt hypothyroidism was defined as high TSH level plus low FT4 level; subclinical hypothyroidism, as high TSH level plus normal FT4 level. Low FT4 level was defined as FT4 level <0.8 ng/dL plus normal TSH level. Subclinical hyperthyroidism was defined as TSH level <0.15 mIU/L with normal FT4 level, while overt hyperthyroidism was defined as TSH level <0.15 mIU/L and FT4 level >1.7 ng/dL.

2.3. Statistical analysis

The difference in the prevalence of hypothyroidism between PI users and non-PI users was tested using the chi-square test. For comparison of multiple risk factors for hypothyroidism, multivariate logistic regression analysis was used. We used the odds ratio (ORs) and 95% confidence interval (95% CI) to estimate the impact of each variable on hypothyroidism. For precise evaluation of the impact of hypothyroidism on BMD loss, first we compared the spine and femoral neck T-scores between patients with hypothyroidism and euthyroidism in both PI users and non-PI users, using the Student's unpaired t-test. Second, for comparison of the impact of biochemical markers associated with hypothyroidism, multivariate linear regression model was used, which included serum-IP, %TRP, LDL-C, iPTH, and vitamin D as independent variables. To evaluate the direct effect of PI on bone turnover, BAP, OC, DPD and u-NTx were compared between PI-users and non-PI users using the Student's unpaired t-test. All statistical analyses were performed with The Statistical Package for Social Sciences ver. 17.0 (SPSS, Chicago, IL).

3. Results

3.1. Patient characteristics and prevalence of hypothyroidism

Table 1 shows the biochemical characteristics of the 184 study patient [8]. Forty of the 184 (22%) patients presented with hypothyroidism. Overt hypothyroidism, subclinical hypothyroidism, and low FT4 were observed in 3 (2%), 7 (4%), and 30 (16%) patients, respectively, whereas hyperthyroidism was diagnosed in only 1 (1%) patient. None of the patients presented with systemic- or

Table 1
Clinical characteristics of the 184 study patients.

Parameter	PI users (n = 117)	Non-PI users (n = 67)	P value
Age, mean (SD)	44.7 (10.4)	44.9 (9.5)	0.908
Body mass index, mean, (kg/m^2)	22.6 (3.1)	22.4 (3.7)	0.713
Hypertension, n (%)	27 (23%)	17 (25%)	0.723
Current smoking, n (%)	69 (59%)	34 (51%)	0.285
History of AIDS-defined illness, n (%)	24 (21%)	9 (13%)	0.318
Current CD4+ T cell count, mean (cells/μL)	504 (217)	497 (234)	0.830
Nadir CD4+ T cell count (cells/μL)	152 (104)	180 (131)	0.117
Low CD4+ T cell count (<200 cells/μL) for >1 year, n (%)	22 (19%)	13 (19%)	0.989
Current suppressed viral load (<20 copies/mL), n (%)	107 (91%)	43 (64%)	<0.001
Current use of ART, n (%)	117 (100%)	53 (79%)	<0.001
Time on ART, months, mean (SD)	92 (74)	87 (72)	0.560
Current use of NNRTI	0 (0%)	26 (39%)	<0.001
Current use of INSTI	1 (1%)	26 (39%)	<0.001
Current use of tenofovir, n (%)	78 (67%)	37 (55%)	0.154
Low eGFR, (<60 mL/min/1.73 m^2)	9 (8%)	1 (1%)	0.096
Low serum phosphorus (<2.0 mg/dL)	1 (1%)	0 (0%)	1.000
Low renal tubular reabsorption of phosphate (<80%)	4 (3%)	1 (1%)	0.655
High LDL-C (>140 mg/dL)	8 (7%)	9 (13%)	0.186
Hyperthyroidism	1 (1%)	0 (0%)	n.a.
Overt hyperthyroidism	0 (0%)	0 (0%)	
Subclinical hyperthyroidism	1 (1%)	0 (0%)	
Hypothyroidism	32 (27%)	8 (12%)	0.016
Overt hypothyroidism	3 (3%)	0 (0%)	
Subclinical hypothyroidism	4 (3%)	3 (4%)	
Low serum thyroxine (<8.0 ng/dL)	25 (37%)	5 (7%)	
High Intact parathyroid hormone (>53 pg/mL)	36 (31%)	20 (30%)	1.000
Low 25 (OH)-Vitamin D (<30 ng/mL)	66 (56%)	40 (60%)	0.416

Values are median (IQR) or number (%) of patients.
ART: antiretroviral therapy, PI: protease inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor, INSTI: integrase inhibitor, eGFR: estimated glomerular filtration rate, LDL-C: low density lipoprotein-cholesterol.