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Authors

Foreman, Sarah C
Wu, Po Hung
Kuang, Ruby
et al.

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Factors associated with bone microstructural alterations assessed by HR-pQCT in long-term HIV-infected individuals

Sarah C. Foreman[a,c], **Po Hung Wu**[a], **Ruby Kuang**[a], **Malcolm D. John**[b], **Phyllis C. Tien**[b], **Thomas M. Link**[a], **Roland Krug**[a], **Galateia J. Kazakia**[a,*]

[a]Department of Radiology and Biomedical Imaging, University of California, San Francisco, 185 Berry Street, Lobby 6, Suite 350, San Francisco, CA 94107, USA

[b]Department of Medicine, University of California, San Francisco, 4150 Clement St, Rm 111W, San Francisco, CA 94121, USA

[c]Department of Radiology, Technical University of Munich, Germany

Abstract

Purpose: In adults with long-term HIV infection, low bone density and increased fracture risk have emerged as significant comorbidities. Our aim was to assess the association of exercise, nutrition, and medications with bone quality in adults with long-term HIV infection.

Methods: Forty-three adults with HIV infection were enrolled (median BMI 25.7, range 18.2–35.6 kg/m^2; median age 57, range 50–69 years). Participants underwent ultradistal radius and tibia high-resolution peripheral quantitative CT (HR-pQCT). Questionnaires included the revised Community Healthy Activities Model Program for Seniors (CHAMPS), the Mini Nutritional Assessment (MNA) as well as medication assessments. Multivariable linear regression models were used to evaluate the association of exercise, nutritional status, tenofovir disoproxil fumarate (TDF) and protease inhibitor (PI) use with bone density and microstructure, adjusting for demographic risk factors.

Results: In regression models, higher nutrition scores were associated with higher tibia cortical thickness ($R^2 = 0.23$; $\beta = 0.03$; $p = 0.044$) and higher radius cortical BMD ($R^2 = 0.43$; $\beta = 8.4$; $p = 0.026$). Higher weekly frequency of all physical activities was significantly associated with higher radius trabecular BMD ($R^2 = 0.38$; p = 0.96; $p = 0.050$), higher radius trabecular number ($R^2 = 0.31$; $\beta = 0.01$; $p = 0.026$), lower tibia and radius trabecular separation (tibia: $R^2 = 0.30$; p = −0.003; $p = 0.038$; radius: $R^2 = 0.35$; $\beta = −0.003$; $p = 0.021$), and higher radius bone stiffness ($R^2 = 0.45$; $\beta = 0.38$; $p = 0.047$). Higher frequency of bone loading physical activities was significantly associated with higher tibia trabecular density ($R^2 = 0.44$; $\beta = 4.06$; $p = 0.036$), higher tibia bone stiffness ($R^2 = 0.46$; = 3.06; $p = 0.050$), and higher tibia estimated failure load ($R^2 = 0.46$; $\beta = 0.17$; $p = 0.049$). TDF used in combination with a PI was associated with lower radius trabecular BMD ($R^2 = 0.39$; $\beta = −41.2$; $p = 0.042$), lower radius trabecular number ($R^2 = 0.34$; $\beta = −0.44$; $p = 0.009$) and greater radius trabecular separation ($R^2 = 0.42$; 0 = 0.16; $p = 0.002$), while TDF use without a PI was not associated with reduced bone quality.

[*]Corresponding author. Galateia.kazakia@ucsf.edu (G.J. Kazakia).

Conclusions: In adults with HIV infection, malnutrition is associated with poor cortical bone quality, while reduced frequency of physical activities and specifically reduced frequency of mechanical loading activities are associated with deficient trabecular bone structure and reduced estimates of bone strength. TDF use in combination with a PI is associated with deleterious effects on trabecular bone structure.

Keywords

HIV; Bone; HR-pQCT; Physical activity; Nutrition

1. Introduction

In adults with long-term human immunodeficiency virus-1 (HIV) infection, low bone mineral density (BMD) and increased fracture risk have emerged as significant comorbidities representing a multifactorial challenge [1–3]. Increased risk of fracture and decreased rate of fracture healing has been shown to significantly affect life expectancy and quality of life [4]. Important contributing factors to the high prevalence of bone disease include overrepresentation of traditional risk factors such as low body mass index (BMI), inactivity, tobacco and alcohol use, poor dietary intake and vitamin D deficiency.

In PLWH low BMD has most commonly been linked to low body weight [5–10]. Despite major improvements in antiretroviral medications leading to significant reductions in the morbidity and mortality of HIV infection, weight loss and wasting remain important problems in PLWH [11]. The etiology of HIV-associated weight loss and wasting is multifactorial. Causes include inadequate dietary intake, altered metabolism, socioeconomic factors, access to care, psychological factors and complications of HIV or side-effects of antiretroviral medication [11]. A meta-analysis showed that on average PLWH were 5.1 kg lighter compared to controls [5], however the effect of malnutrition and low body weight on bone structure and microstructure in PLWH is not well understood.

Regular physical activity is recommended for optimal bone health in the general population [12]. Although physical activity likely has similar effects in PLWH, research on the impact of physical activity on bone loss in PLWH has been limited. Bonato et al. enrolled 27 PLWH and documented changes in BMD after a moderate-aerobic exercise [brisk walking] intervention of 12 weeks [13]. They found improved spinal BMD, as well as femoral BMD [13]. Santos et al. measured changes in BMD in 20 adults with HIV and lipodistrophy who participated in a 12-week strength training intervention (36 sessions), resulting in improved BMD at the lumbar spine and femoral neck and the radius [14].

Another factor predisposing people living with HIV (PLWH) to bone loss is the lifelong treatment with antiretroviral therapy. Standard antiretroviral therapy consists of the combination of at least three antiretroviral drugs to suppress the HIV virus and reduce disease related complications and the risk of HIV transmission [15], Antiretroviral therapy has been shown to trigger adverse osteogenic effects, either indirectly-through renal phosphorous wasting and hyperparathyroidism - or directly - through stimulation of osteoclastogenesis [16–18]. A previous study demonstrated that BMD decreases by 2%−6%

within the first 2 years of antiretroviral therapy initiation, regardless of the choice of therapy [19].

Regarding the influence of disease severity on bone health, contradicting results were found by two studies measuring disease severity with CD4 count [20,21], Sawlani et al. found lower CD4 count to be associated with reduced BMD, while Biver et al. found no significant difference [20,21]. However, the mechanism and extent of how nutrition, physical activity, antiretroviral therapy and disease severity influence bone quality, and in particular bone microstructure, in long-term HIV seropositive individuals is not yet well understood.

While DXA (dual-energy X-ray absorptiometry) is the gold standard to measure areal BMD (aBMD) and to clinically assess bone fragility [22], it cannot provide information on cortical and trabecular compartments individually, nor quantitative microarchitecture information [23]. High-resolution peripheral quantitative computed tomography (HR-pQCT) provides measurements of both bone quality and mass of the cortical and trabecular compartments including bone microstructure [24]. A previous study comparing bone quality in PLWH to uninfected controls only detected impaired trabecular bone microstructure with HR-pQCT but no differences in aBMD by DXA, indicating that HR-pQCT may be more sensitive than DXA for the assessment of bone health in this population [25].

The aim of this study was therefore to analyze the association of nutrition, physical activity, antiretroviral medications, and HIV disease severity with bone density and microarchitecture measured using HR-pQCT in long-term HIV seropositive individuals. These data will inform efforts to identify treatment and prevention strategies to ultimately reduce the prevalence of bone loss and fracture risk in the aging HIV population.

2. Materials and methods

2.1. Study participants

Forty-three HIV seropositive adults were enrolled in our study, all with known HIV infection for   7 years. All participants were on a stable antiretroviral therapy regimen in the prior year. Informed consent was obtained from all participants; the study was compliant with the Health Insurance Portability and Accountability Act and approved by the local institutional review board.

Participants with chronic diseases associated with poor bone quality such as diabetes mellitus, rheumatologic diseases, chronic kidney disease, malabsorption syndromes and hepatitis C virus (HCV) infection were excluded. Participants treated with medications known to impact bone and mineral metabolism including current use of calcitonin, systemic glucocorticoids, thiazolidinedione, thyroid hormone replacement, and use of bisphosphonate or teriparatide in the last year or for > 12 months ever were also excluded. We further excluded participants with fractures at the imaging sites, an episode of immobilization lasting longer than 1 week in the previous six months, with conditions excluded by x-ray safety guidelines, illicit drug use and pre- or perimenopausal women (last menses   3 years). The target age range for enrollment was 50–70 years.

2.2. Medical history and clinical examination

The following information was obtained from patient records or recorded at study visit: Duration of HIV infection, disease complications, current medications including supplements containing vitamin D and/or calcium, alcohol or tobacco use, and history of fractures including history of low impact trauma fractures.

Participants completed the Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire [26,27], to assess the associations of bone microarchitecture and weekly frequency of participation in physical activities. Study participants were asked to self-report whether they had engaged in 27 light, moderate, and vigorous physical activities to which participants reported their weekly frequency of participation in a typical week over the last 4 weeks. Frequency measures were calculated as a sum of frequency per week for all activities (light, moderate, and vigorous). Given the importance of mechanical loading for bone adaptation [28–31], we also assessed the association of frequency of all bone-loading physical activities and frequency of upper body loading activities.

The Mini Nutritional Assessment (MNA) was used to determine nutritional status. The MNA is a validated nutritional assessment tool for older people [32–36], consisting of self-reported questions derived from four parameters of assessment: anthropometric assessment, general assessment, dietary assessment and self-assessment. The questionnaire permits detection of a decline in ingestion (loss of appetite, decline of food intake, digestive problems, chewing or swallowing difficulties), weight loss, current mobility impairment, acute illness or major stress in the past three months, neuropsychological problems (dementia or depression) and a decrease in BMI. The following scoring system is used: normal nutritional status [12–14], at risk of malnutrition [8–11] and malnourished (0–7) [37].

HIV-related laboratory parameters (current CD4 cell count and HIV-RNA within 3 months of the study visit) were obtained from clinical records.

2.3. HR-pQCT bone imaging and quantification

All participants were imaged using a HR-pQCT system (XtremeCT, Scanco Medical AG, Bruttisellen, Switzerland), according to the manufacturer's standard in vivo protocols (60 kVp, 900 μA, 100 ms integration time, 750 projections over 180°). HR-pQCT images were obtained at 82 μm nominal voxel size in 9.02 mm stack lengths, at theultra-distal radius (starting 9.5 mm proximal to the distal endplate) and ultra-distal tibia [starting 22.5 mm proximal to the distal endplate), as described in detail elsewhere [38]. The non-dominant extremity was scanned unless there was a history of injury or surgery at that location. Trabecular and cortical density and structure parameters were quantified from these images using the manufacturer's standard in vivo analysis protocol [38–40]. Linear micro-finite element (μFF.) analysis was performed to calculate apparent biomechanical properties (Scanco FE Software Version 1.12, Scanco Medical AG) using previously described techniques [41–43]. Homogeneous properties were assumed for all bone elements, with each element assigned an elastic modulus of 6 GPa and a Poisson ratio of 0.3 [41]. A uniaxial

compression test in the superinferor direction was performed with an applied strain of 1%. Failure load was estimated using methods validated by Mueller and colleagues [41]; failure was reached when a 7.5% critical bone volume reached a 0.7% strain threshold. From these analyses, the following quantitative trabecular and cortical parameters were obtained for tibia and radius, respectively: trabecular density, trabecular number, trabecular separation, cortical density, and cortical thickness. To provide an estimate of bone strength we also included the parameters bone stiffness and estimated failure load for the tibia and radius, respectively.

Reproducibility measurements previously obtained in elderly subjects in our facility indicated the least significant change and root mean square coefficient of variation LSC (RMSCV) for cortical density of the tibia to be 14 mg HA/cm^3 (0.6%), for cortical thickness of the tibia 50 μm (1.5%), for cortical density of the radius 17 mg HA/cm^3 (0.8%), and for cortical thickness of the radius 80 μm (3.9%) [39], LSC and RMSCV for trabecular parameters are lower than for cortical parameters [44].

2.4. DXA evaluation

DXA exams of the femur and lumbar spine were obtained as part of standard clinical care in 37 participants (13 participants: Prodigy, GE/Lunar, Milwaukee, WI, USA; 24 participants: Horizon A, Hologic, Marlborough, MA, USA). Areal BMD was automatically calculated at the proximal femur (femur neck and total femur) and the lumbar spine (Ll-4). Fractured vertebrae and degenerated segments were excluded from the analysis. Online available conversion tables from the manufacturers were used to convert aBMD values between the different scanners.

2.5. Statistical analysis

Statistical analysis was performed with SPSS software (version 23; IBM, Armonk, NY, USA), using a 2-sided 0.05 level of significance. Multivariable linear regression models were used to evaluate the associations of nutritional status, physical activity (frequency of all activities, frequency of all bone loading activities, and frequency of upper body loading activities), disease severity (duration of HIV infection, CD4 count, and HIV viral load), and antiretroviral therapy on bone density and microarchitecture, adjusting all models for age, sex, and race. For the regression analysis nutritional status, physical activity, and CD4 count were Included as continuous variables; HIV viral load, duration of HIV infection, and use of antiretroviral medications were included as categorical variables. HIV viral load was included as a categorical variable (not detectable i.e. HIV RNA < 40 copies/ml vs. detectable). Duration of HIV infection was included as a categorical variable (under 20 years vs. over 20 years). We analyzed the associations of two specific antiretroviral medications (tenofovir disoproxil fumarate and protease inhibitors), that were previously shown to particularly affect bone structure [45–49]. We analyzed [1] the use of regimens including tenofovir disoproxil fumarate vs. the use of regimens not including tenofovir disoproxil fumarate, [2] the use of regimens including a protease inhibitor vs. the use of regimens not including a protease inhibitor, and [3] the use of regimens including both tenofovir disoproxil fumarate and a protease inhibitor vs. regimens not including the combination of tenofovir disoproxil fumarate and a protease inhibitor. Due to the explorative nature of

this study, no adjustments were made for multiple testing. Physical activity and nutritional status were considered primary predictors. Disease severity parameters and medication on bone microarchitecture were considered secondary predictors. This analysis strategy was also applied to DXA data to evaluate the associations of nutritional status, physical activity, disease severity, and antiretroviral medication on DXA-derived aBMD.

3. Results

3.1. Study participants

The median age of participants in this study was 57.0 years (range 50–69), with a median BMI of 25.7 kg/m^2 (range 18.2–35.6) and more males (86%, 37/43) than females. The racial distribution consisted of 79% (34/43) Caucasian participants, 19% (8/43) African-American participants, and one Asian participant. None of the participants reported current HIV associated disease complications. Previous reported HIV associated complications included one case of extensive leukoencephalopathy (Balint's syndrome), six cases of anal low grade squamous intraepithelial lesions, one case of anal squamous cell carcinoma and one case of limited cutaneous Kaposi sarcoma. None of the participants were coinfected with either hepatitis B virus (HBV) or HCV. This was defined as a negative blood test for anti-HCV/ anti-HBV antibodies and HBV antigenes, or HCV ribonucleic acid (RNA)/HBV desoxyribonucleic acid (DNA). Seven participants reported a previous fracture (5 wrist fractures, 1 mandibular fracture, 1 humerus fracture). The humerus fracture was caused by a fall from standing height (low impact trauma). The other fractures were reported to be caused by high-impact trauma: the wrist fractures were caused by bicycle accidents ($n = 2$), in-line skating ($n = 1$), a motor vehicle accident (n = 1) and a skiing accident (n = 1); the mandibular fracture was caused by direct trauma (hit from the side). Participant characteristics are demonstrated in Table 1.

3.2. Nutritional status

The mean MNA nutrition score was 12 ± 2.2; range 7–14. Two participants (2/43, 5%) met the definition of malnutrition (MNA score 0–7); 28% (12/43) were at risk of malnutrition (MNA score 8–11). The association of nutritional status and bone parameters is shown in Table 2 and representative images are presented in Fig. 1. In models adjusted for age, sex, and race, significant associations were found between higher nutritional scores and higher tibia cortical thickness ($R^2 = 0.23$; coefficient: 0.03; 95% confidence interval (CI): 0.01, 0.065; $p = 0.044$). Furthermore, radius cortical BMD was significantly higher in these participants ($R^2 = 0.43$; coefficient: 8.4; 95% CI: 1.0, 15.8; $p = 0.026$), Supplementary figures. Interestingly, no significant association was found between nutritional scores and trabecular HR-pQCT parameters ($p > 0.05$). Nutritional scores showed no significant associations with DXA aBMD measurements, Supplementary material Table 1.

3.3. Physical activity

The mean weekly frequency for all activities in a typical week was 21 ± 10 events per week. The mean weekly frequency for bone-loading activities in a typical week was 1.9 ± 1.6 events per week. The mean weekly frequency upper-body loading activities in a typical week was 1.3 ± 1.8 events per week. The associations of weekly frequency of

physical activities on bone parameters are summarized in Table 3. In models adjusted for age, sex, and race, greater frequency of physical activity was significantly associated with more robust trabecular bone at both the radius and tibia and higher estimates of bone strength. Higher frequency of all physical activities (light, moderate, and vigorous) was significantly associated with higher radius trabecular density ($R^2 = 0.38$; coefficient: 0.96; 95% Cl: 0.001, 1.93; $p = 0.050$) and higher radius trabecular number ($R^2 = 0.31$; coefficient: 0.01; 95% Cl: 0.001, 0.02; $p = 0.026$). Moreover, higher frequency of all physical activities was significantly associated with lower tibia and radius trabecular separation ($R^2 = 0.30$; coefficient: −0.003; 95% Cl: −0.01, 0.00; $p = 0.038$ and $R^2 = 0.35$; coefficient: −0.003; 95% Cl: −0.01, 0.00; $p = 0.021$, respectively) and higher radius bone stiffness ($R^2 = 0.45$; coefficient: 0.38; 95% Cl: 0.01, 0.75; $p = 0.047$). Higher frequency of all bone loading physical activities was significantly associated with higher tibia trabecular density ($R^2 = 0.44$; coefficient: 4.06; 95% Cl: 0.29, 7.84; $p = 0.036$), higher tibia bone stiffness ($R^2 = 0.46$; coefficient; 3.06; 95% Cl; 0.00, 6.12; $p = 0.050$), and higher tibia estimated failure load ($R^2 = 0.46$; coefficient: 0.17; 95% Cl: 0.00, 0.34; $p = 0.049$). Higher frequency of upper body loading activities had a trend towards higher radius trabecular number ($R^2 = 0.26$; coefficient: 0.04; 95% Cl: 0.01, 0.09; $p = 0.086$) and lower radius trabecular separation ($R^2 = 0.30$; coefficient: −0.01; 95% Cl: −0.03, 0.00; $p = 0.074$). No associations were found between physical activity and cortical HR-pQCT parameters ($p > 0.05$). Moreover, no significant associations were found between physical activity parameters and DXA aBMD measurements (Supplementary material Table 1).

3.4. Disease severity and antiretroviral medication

The mean duration of HIV infection (time since diagnosis) was 22 ± 8.4 years (range 7–39). Thirty-nine participants were suppressed on successful antiretroviral therapy (HIV RNA < 40 copies/ml; four participants had 44, 45, 58, and 214 detected copies/ml, respectively. The mean CD4 cell count was 657 ± 289 (range 119–1228). In models adjusted for age, sex, and race, participants with HIV infection > 20 years ($n = 26$) had significantly lower trabecular BMD of the radius ($R^2 = 0.43$; coefficient: −25.7; 95% Cl: −47.0, −4.32; $p = 0.020$), reduced cortical thickness of the radius (R^2 −0.33; coefficient: −0.13; 95% Cl; −0.25, −0.002; $p = 0.046$), reduced radius bone stiffness ($R^2 = 0.51$; coefficient: −10.6; 95% Cl; −18.9, −2.3; $p = 0.014$), and lower radius estimated failure load ($R^2 = 0.40$, coefficient: −0.68; 95% Cl: −1.3, −0.08; $p = 0.028$) compared to participants with HIV infection 20 years. In models adjusted for age, sex, and race, CD4 count and detectable viral load were not significantly associated with cortical or trabecular HR-pQCT parameters ($p > 0.05$).

Regarding medications, in models adjusted for age, sex, and race, the use of regimens including the combination of tenofovir disoproxil fumarate and a protease inhibitor was significantly associated with lower trabecular BMD of the radius ($R^2 = 0.39$; coefficient: −41.2; 95% Cl: −80.8, −1.6; $p = 0.042$), lower radius trabecular number ($R^2 = 0.34$; coefficient: −0.44; 95% Cl: −0.76, −0.11; $p = 0.009$), and greater radius trabecular separation ($R^2 = 0.42$; coefficient: 0.16; 95% Cl: 0.06, 0.26; $p = 0.002$), compared to the use of regimens not including the combination of tenofovir disoproxil fumarate and a protease inhibitor. The use of tenofovir disoproxil fumarate or use of a protease inhibitor alone was not associated with lower bone quality. The associations of medication and

bone microarchitecture are shown in Table 4. Disease severity parameters and antiretroviral therapy medication showed no significant associations with DXA aBMD measurements (Supplementary material Table 1).

4. Discussion

This study examined factors associated with alterations of cortical and trabecular bone and estimates of bone strength in long term HIV seropositive individuals using HR-pQCT. We found an association of malnutrition with poor cortical bone quality in PLWH, while reduced frequency of physical activities and specifically reduced frequency of mechanical loading activities were associated with deficient trabecular bone structure and reduced estimates of bone strength. Moreover, longer duration of HIV infection and use of tenofovir disoproxil fumarate in combination with a protease inhibitor were associated with deficient cortical and trabecular bone structure and reduced estimates of bone strength.

Lower nutrition scores were associated with poor cortical bone quality in our cohort of adults with long-term HIV infection. Cortical bone is an important determinant of whole bone strength and fracture risk [50,51], substantially contributing to biomechanical load bearing in elderly subjects, in whom a large part of the trabecular compartment has been resorbed [52]. Therefore, adults with HIV at risk of malnutrition would likely benefit from nutritional support to abate deficiencies in cortical bone structure, improve biomechanical properties, and ultimately reduce the associated fracture risk. In postmenopausal women low body weight and weight-loss are also considered risk factors for osteoporosis, while weight gain appears to protect against bone loss [53]. Previous studies showed that specific dietary recommendations such as increased calcium and vitamin D intake and reduced salt and protein intake can reduce bone loss and decrease fracture risk in the general population [54]. These interventions could likely be translated into the population of PLWH. However, since the causes for malnutrition and weight loss in PLWH are multifactorial, other moderating factors such as access to care, socioeconomic factors or factors linked to médication side-effects would need to be taken into consideration.

Our findings that higher frequency of all physical activity (light, moderate, and vigorous) may attenuate decreases in BMD are in agreement with longitudinal studies of populations at high risk for bone loss (e.g., postmenopausal women) showing that consistent participation in physical activity is associated with reduced bone loss [55–58]. Furthermore, strength training (including any strength training in the last week) has been shown to reduce bone loss in PLWH [10], Bonato et al. enrolled 27 PLWH and documented changes in BMD after a moderate-aerobic exercise (brisk walking) intervention of 12 weeks [13], They found improved spinal BMD, as well as femoral BMD [13]. Santos et al. tested a 12-week strength training intervention in 20 adults with HIV and lipodystrophy [14] and found that participants had significant increases in BMD at the lumbar spine, femoral neck and radius at the end of the intervention [14]. The strength training was composed by the following exercises: warm-up (active stretching), bench press, lat pull-down, leg extension, leg flexion, elbow flexion, elbow extension, abdominal exercise, sole flexion, and cool-down (active stretching) [14]. While these studies only included small sample sizes, they produced promising foundational evidence for the efficacy of physical activity interventions

to improve BMD and prevent bone loss in PLWH [13,14]. In addition exercise interventions for other at-risk populations could be used in PLWH including training programs that induce stress to the skeleton by means of either ground-reaction or muscle-induced forces [59].

Concerning the effects of exercise on bone microstructure, previous studies with cohorts of postmenopausal women found that increased amounts of total physical activity (light, moderate, and vigorous) mainly maintains cortical bone rather than trabecular bone components [53,56]. Another review concluded that increased amounts of total physical activity maintains both cortical and trabecular components [57]. To the best of our knowledge only one study evaluated the association of bone microarchitecture and exercise assessed by frequency questionnaires in PLWH (no specific information was provided on which questionnaire was used). In analyses including 28 HIV positive and 112 HIV negative participants, physical activity was significantly associated with higher trabecular and cortical parameters (adjusted for age and BMI), however not significantly associated with bone microarchitecture parameters in analyses adjusted for age, BMI and HIV status [21].

Previous studies by Robling et al. have shown that short periods of exercise with rest periods in between are more effective to prevent bone loss compared to a single sustained exercise session [28,29,31]. Bone cells have been shown to desensitize after a few minutes of loading with the cellular response subsequently reducing. Moreover, higher levels of cortisol caused by high volumes and intensities of exercise potentially increase catabolic actions on bone [60]. Physical activities specifically targeting mechanical loading were previously shown to be a particularly potent stimulus for bone cells [30]. These findings are in line with the results of our study showing that higher frequency of bone loading activities was significantly associated with higher tibia trabecular density, higher tibia bone stiffness, and higher tibia estimated failure load.

We found different relationships between the weight-bearing tibia and the non-weightbearing radius in our study population. As expected those more frequently engaging in upper body loading activities (e.g. tennis) showed a trend towards higher trabecular number and lower trabecular separation at the radius. However the reason for differing relationships for nutrition and antiretroviral medications are unclear. Moreover, those with HIV infection over 20 years had significantly worse trabecular and cortical parameters, and reduced estimates of bone strength, only at the radius but not at the tibia. As models were adjusted for age, the association does not seem to be influenced by the fact that those with HIV infection over 20 years might be older. These findings indicate that after long-term HIV-infection, bone loss is exacerbated at non-weightbearing sites but maintained at weightbearing sites. However, further studies conducting analyses of bone microarchitecture at multiple time points and anatomic sites are warranted to evaluate longitudinal changes.

In accordance with previously published studies [10,21] we detected no significant associations of CD4 count with parameters of bone quality. Sawlani et al. found a correlation of low CD4 count and low BMD levels [20]. However, it should be noted that the mean CD4 count observed by Sawlani et al. (281 ± 113) was notably lower compared to our mean CD4 count [657 ± 289]. Therefore, it seems plausible that disease severity could detrimentally

affect bone density in adults with particularly low CD4 count, while not in adults with a CD4 count above a certain level.

Antiretroviral therapy combinations including tenofovir disoproxil fumarate have previously been associated with increased bone loss and higher fracture risk in adults with HIV infection [45–47]. Moreover, a randomized, double-blind, placebo-controlled trial evaluating tenofovir disoproxil fumarate/Emtricitabine pre-exposure prophylaxis among HIV-negative men found that those randomized to tenofovir disoproxil fumarate/Emtricitabine demonstrated greater decreases in BMD than those randomized to the placebo arm [49]. Tenofovir disoproxil fumarate plasma concentrations have been shown to be increased when combined with protease inhibitors [47,48], therefore potentially increasing detrimental effects on bone composition. We identified the combined use of tenofovir disoproxil fumarate with a protease inhibitor to be associated with lower trabecular bone quality, while tenofovir disoproxil fumarate use or protease inhibitor use alone were not associated with bone quality deterioration. Therefore, as expected, avoiding this specific medication combination could reduce the fracture risk in PLWH.

In our previous publication we found that HR-pQCT is a powerful tool to assess bone health in HIV-infected men who show no differences to healthy males by DXA aBMD [25], With this new cohort and in the context of questions about nutrition, exercise, antiretroviral therapy medications, and disease severity, our results replicated these previous findings, supporting the conclusion that DXA may be less useful for the evaluation of bone structure in PLWH.

Some limitations are pertinent to this study. While information on current viral load and CD4 count were available, current testosterone levels were unknown; therefore the influence of testosterone level on bone quality could not be assessed. Moreover, we did not have sufficient information on previous disease control and this may also have an effect on bone parameters, given the mean disease duration of 22 years. Another limitation is that only three participants in our study were currently using regimens including tenofovir disoproxil fumarate and a protease inhibitor, because in the past few years physicians have typically changed regimens including this combination due to the known detrimental effects on bone structure. However, this medication combination was of specific interest for this exploratory study because tenofovir disoproxil fumarate plasma concentrations have been shown to increase when combined with protease inhibitors [47,48]. Studies including larger groups of participants on this specific regimen would be necessary to replicate this finding. Finally, because physical activity was assessed using questionnaires, we cannot fully exclude a certain extent of response bias. To minimize socially desirable responding and overreporting of physical activities we used the CHAMPS questionnaire. This questionnaire includes a number of questions on activities other than physical activities in the list, subsequently enabling individuals who are less physically active to report participation in other types of valued activities (e.g. volunteering, attending church, visiting friends, playing a musical instrument) and thus minimizing the likelihood of less active individuals having to report "no" to the majority of questions [26].

5. Conclusions

In conclusion, in the context of HIV infection, regular exercise could help maintain or improve trabecular bone structure and bone strength while nutritional support is specifically relevant for maintaining cortical bone structure. Patients on specific antiretroviral therapy combinations such as tenofovir disoproxil fumarate and protease inhibitors may require close monitoring to assess bone loss and extent of fracture risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Abbreviations:

HIV	human immunodeficiency virus-1
BMD	bone mineral density
BMI	body mass index
PLWH	people living with HIV
HR-pQCT	high-resolution peripheral quantitative computed tomography
DXA	dual-energy x-ray absorptiometry
aBMD	areal BMD
HCV	hepatitis C virus
HBV	hepatitis B virus
LSC	least significant change
RMSCV	root mean square coefficient of variation

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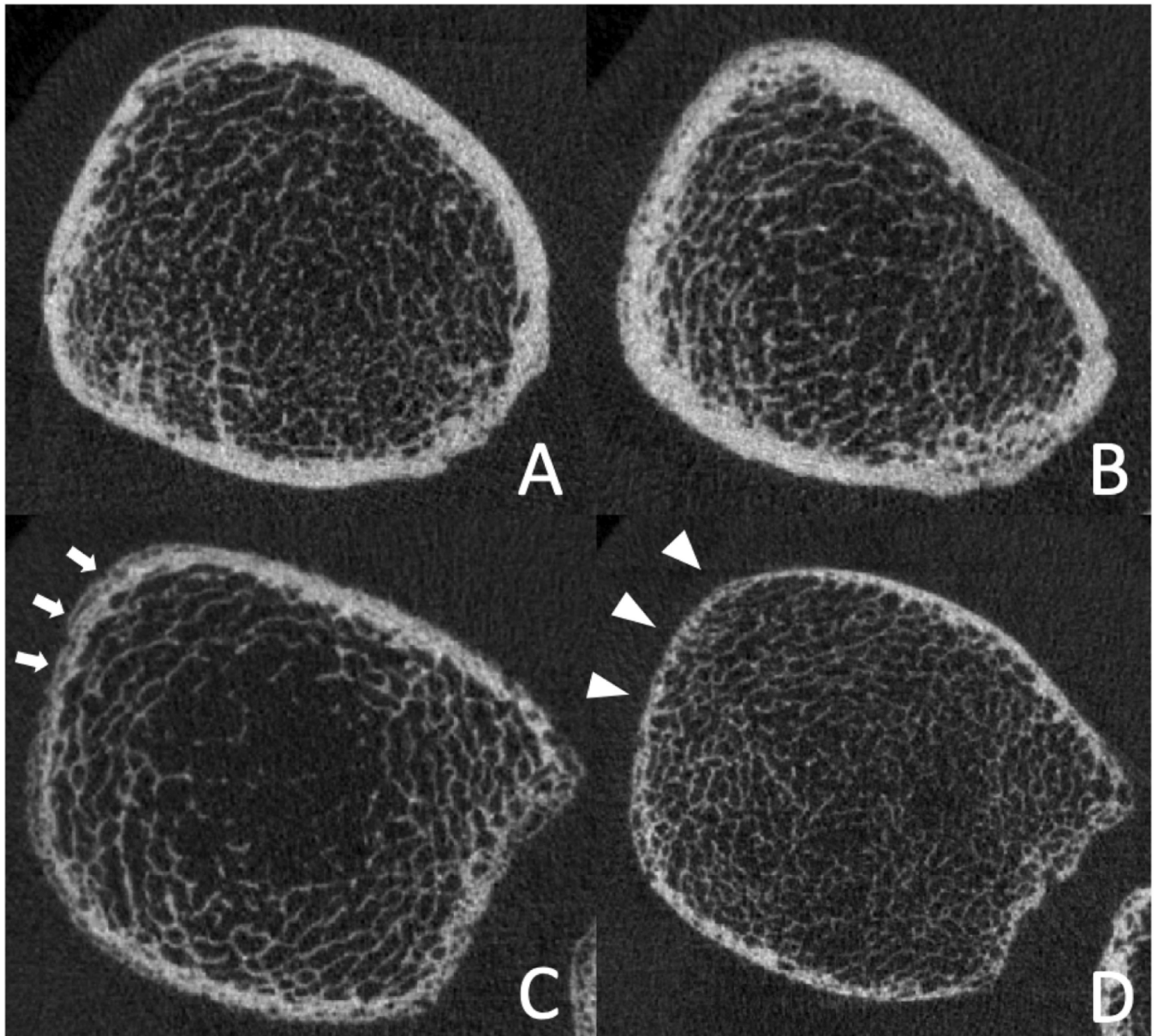
Fig. 1.
Ultradistal tibia HR-pQCT images of two adults with HIV-infection with high nutritional scores (A: 53 years, male, white, 167 cm; B: 52 years, male, white, 170 cm) and two adults with HIV-infection with low nutritional scores (C: 55 years, male, white, 171 cm; D: 57 years, male, white, 168 cm). Those with low nutritional scores show reduced cortical BMD with visibly higher porosity (C, white arrows) and reduced cortical thickness (D, white arrowheads).

Table 1

Subject characteristics.

Subject characteristics	n = 43
Age[a]	57.0 (54;62)
Sex	
Females	14%
Males	86%
Body mass index in kg/m2[a]	25.7 (21.6;26.7)
Race	
Caucasian	79%
African American	19%
Asian	2%
Risk factors	
Current tobacco consumption	19%
Alcohol consumption ≥ 7 units weekly	12%
Supplements	
Calcium	23%
Vitamin D	42%
HIV characteristics	
Time since diagnosis in years[a]	24.0 (20;27)
HIV-RNA < 40 copies	93%
CD4 cell count in cells/μl[a]	644 (316;804)
Percentage of participants on antiretroviral therapy regimens (HIV therapies) including the following antiretroviral medications[b]:	
Nucleoside reverse-transcriptase inhibitors	98%
Integrase inhibitors	51%
Non-nucleoside reverse-transcriptase inhibitors	47%
Tenofovir alafenamide	44%
Tenofovir disoproxil fumarate	35%
Protease inhibitor	26%
Tenofovir disoproxil fumarate and protease inhibitor	

[a]Numbers are median (25th and 75th percentiles).

[b]All participants were on more than one type of antiretroviral medication, therefore numbers do not add lip to 100%.

Table 2

Association between nutritional status and bone microarchitecture.

Parameter (n = 43)	Nutritional status			
	R^2 base model[a]	R^2 (p)[b]	β value[c]	p-Value[*d]
Tibia				
Trabecular density	0.36	0.36	−0.12	0.955
		(0.005)	(−4.3;4.0)	
Trabecular number	0.18	*ns*	*ns*	*ns*
Trabecular separation	0.21	*ns*	*ns*	*ns*
Cortical density	0.28	0.33 (0.010)	*7.1* (−1.7;16.0)	0.112
Cortical thickness	0.14	0.23 (0.071)	0.03 (0.001;0.07)	**0.044**
Bone stiffness	0.40	0.40 (0.001)	1.0 (−2.3;4.3)	0.539
Failure load	0.40	0.41 (0.001)	0.04 (−0.15;0.22)	0.686
Radius				
Trabecular density	0.31	0.32 (0.016)	−1.7 (−6.6;3.1)	0.472
Trabecular number	0.20	0.23 (0.088)	−0.03 (−0.07;0.02)	0.226
Trabecular separation	0.24	0.28 (0.037)	0.01 (−0.004;0.02)	0.162
Cortical density	0.34	0.43 (0.001)	8.4 (1.0;15.8)	**0.026**
Cortical thickness	0.24	0.24 (0.082)	0.004 (−0.03;0.03)	0.800
Bone stiffness	0.38	0.38 (0.004)	−0.05 (−2.1;2.0)	0.961
Failure load	0.29	0.29 (0.029)	−0.01 (−0.16;0.14)	0.917

ns: $p > 0.1$ for total model and individual predictor, respectively.

[a]R^2 for base model (age, sex, race).

[b]R^2 and p-value for total model.

[c]Multivariable linear regression adjusting for age, sex and race.

[d]p-Value for individual predicor (nutritional status).

[*]Significant ($p < 0.05$) values are in bold.

Table 3

Association between frequency of physical activities and bone microarchitecture.

Parameter (n = 43)	R² base model[a]	Frequency of all physical activities			Frequency of bone-loading physical activities			Frequency of upper-body bone-loading physical activities		
		R² (p)[b]	β value[c]	p-value*[d]	R² (p)[b]	β value[c]	p-value*[d]	R² (p)[b]	β value[c]	p-value*[d]
Tibia										
Trabecular density	0.36	0.36 (0.005)	0.07 (−0.81;0.95)	0.871	0.44 (0.001)	4.06 (0.29;7.84)	**0.036**	0.37 (0.004)	1.58 (−3.73;6.90)	0.551
Trabecular number	0.18	0.24 (0.074)	0.01 (−0.002;0.02)	0.119	0.24 (0.063)	0.04 (−0.01;0.08)	0.093	ns	ns	ns
Trabecular separation	0.21	0.30 (0.023)	−0.003 (−0.01;0.00)	**0.038**	0.27 (0.036)	−0.01 (−0.03;0.001)	0.074	0.23 (0.080)	−0.01 (−0.03;0.01)	0.270
Cortical density	0.28	0.28 (0.032)	−0.07 (−2.03;1.90)	0.945	0.29 (0.027)	3.0 (−5.9;11.9)	0.503	0.29 (0.025)	−4.59 (−16.4;7.25)	0.437
Cortical thickness	0.14	ns	ns	ns	ns	ns	ns	ns	ns	ns
Bone stiffness	0.40	0.40 (0.002)	−0.10 (−0.81;0.60)	0.769	0.46 (0.000)	3.06 (0.00;6.12)	**0.050**	0.40 (0.002)	0.66 (−3.6;4.9)	0.757
Failure load	0.40	0.40 (0.002)	−0.00 (−0.04;0.04)	0.920	0.46 (0.000)	0.17 (0.001;0.34)	**0.049**	0.41 (0.002)	0.05 (−0.19;0.29)	0.666
Radius										
Trabecular density	0.31	0.38 (0.004)	0.96 (0.001;1.93)	**0.050**	0.34 (0.011)	2.76 (−1.77;7.29)	0.225	0.34 (0.010)	3.88 (−2.15;9.90)	0.200
Trabecular number	0.20	0.31 (0.021)	0.01 (0.001;0.02)	**0.026**	0.23 (0.084)	0.02 (−0.01;0.06)	0.208	0.26 (0.049)	0.04 (−0.01;0.09)	0.086
Trabecular separation	0.24	0.35 (0.009)	−0.003 (−0.01;0.00)	**0.021**	0.27 (0.039)	−.01 (−0.02;0.00)	0.183	0.30 (0.022)	−0.01 (−0.03;0.00)	0.074
Cortical density	0.34	0.36 (0.007)	0.77 (−0.70;2.24)	0.297	0.36 (0.008)	2.88 (−4.59; 10.4)	0.438	0.34 (0.011)	0.96 (−8.12; 10.0)	0.831
Cortical thickness	0.24	0.29 (0.030)	0.004 (−0.001;0.01)	0.114	0.25 (0.074)	0.01 (−0.02;0.04)	0.564	0.24 (0.084)	−0.001 (−0.04;0.03)	0.957
Bone stiffness	0.38	0.45 (0.001)	0.39 (0.01;0.75)	**0.047**	0.40 (0.003)	0.96 (−1.0; 2.96)	0.326	0.39 (0.003)	0.84 (−1.5;3.2)	0.478
Failure load	0.29	0.46 (0.001)	0.02 (0.00;0.04)	0.054	0.41	0.05 (−0.06;0.16)	0.359	0.40 (0.003)	0.05 (−0.09;0.18)	0.497

ns: p > 0.1 for total model and individual predictor, respectively.

[a] R² for base model (age, sex, race).

[b] R² and p-value for total model.

[c] Multivariable linear regression adjusting for age, sex and race.

[d] p-Value for individual predicor (frequency of all physical activities/bone-loading physical activities/upper-body loading physical activities).

* Significant (p < 0.05) values are in bold.

Table 4

Association between antiretroviral medications and bone microarchitecture.

Parameter (n = 43)	R² base model[a]	TDF			PI			TDF and PI		
		R² (P)[b]	ß value[c]	p-Value*[d]	R² (P)[b]	ß value[c]	p-Value*[d]	R² (P)[b]	ß value[c]	p-value*[d]
Tibia										
Trabecular density	0.36	0.36 (0.005)	3.5 (−16.3;23.3)	0.723	0.36 (0.005)	0.39 (−20.1;20.9)	0.969	0.36 (0.005)	−1.10 (−37;35)	0.951
Trabecular number	0.18	0.24 (0.064)	−0.17 (−0.39;0.04)	0.107	ns	ns	ns	ns	ns	ns
Trabecular separation	0.21	0.26 (0.046)	0.06 (−0.02;0.13)	0.126	0.22 (0.089)	−0.03 (−0.11;0.05)	0.417	0.22 (0.096)	0.05 (−0.09;0.19)	0.486
Cortical density	0.28	0.30 (0.019)	21.7 (−21.8;65.2)	0.318	0.35 (0.006)	42.3 (−0.86;86)	0.054	0.34 (0.007)	72 (−4.6;148)	0.065
Cortical thickness	0.14	ns	ns	ns	0.22 (0.092)	0.15 (−0.01;0.21)	0.064	0.22 (0.086)	0.27 (−0.01;0.55)	0.058
Bone stiffness	0.40	0.40 (0.001)	3.9 (−11.9;19.7)	0.620	0.44 (0.001)	12.6 (−3.2;28.4)	0.116	0.43 (0.001)	19.1 (−8.9; 47.1)	0.176
Failure load	0.40	0.40 (0.001)	0.09 (−0.79;0.98)	0.833	0.44 (0.000)	0.69 (−0.19; 1.58)	0.121	0.42 (0.001)	0.91 (−0.67;2.48)	0.251
Radius										
Trabecular density	0.31	0.31 (0.018)	−5.56 (−29.1;18.0)	0.635	0.34 (0.010)	−15.4 (−38.6;7.9)	0.188	0.39 (0.003)	−41.2 (−80.8; −1.6)	**0.042**
Trabecular number	0.20	ns	ns	ns	ns	ns	ns	0.34 (0.010)	−0.44 (−0.76;−0.11)	**0.009**
Trabecular separation	0.24	0.27 (0.048)	0.04 (−0.03;0.10)	0.250	0.27 (0.042)	0.04 (−0.02;0.10)	0.201	0.42 (0.001)	0.16 (0.06;0.26)	**0.002**
Cortical density	0.34	0.35 (0.010)	−4.53 (−39.2;30.1)	0.792	0.37 (0.006)	19.7 (−15.6;55.1)	0.264	0.37 (0.006)	34.6 (−26;95)	0.253
Cortical thickness	0.24	0.25 (0.070)	−0.04 (−0.17;0.9)	0.502	0.26 (0.061)	0.06 (−0.07;0.19)	0.372	0.25 (0.069)	0.08 (−0.15;0.31)	0.482
Bone stiffness	0.38	0.39 (0.004)	−2.6 (−11.7;6.5)	0.567	0.38 (0.004)	0.70 (−8.8; 10.2)	0.881	0.39 (0.004)	−1.8 (−18.1;14.4)	0.820
Failure load	0.29	0.29 (0.029)	−0.01 (−0.65;0.63)	0.975	0.29 (0.028)	0.10 C−0.57;0.77)	0.757	0.29 (0.029)	−0.14 (−1.3;1.0)	0.806

ns: p > 0.1 for total model and individual predictor, respectively; abbreviations: tenofovir disoproxil fumarate (TDF), protease inhibitor (PI). Abbreviations: TDF (tenofovir disoproxil fumarate); PI (protease inhibitor).

[a] R²-2 for base model (age, sex, race).

[b] R²-2 and p-value for total model.

[c] Multivariable linear regression adjusting for age, sex and race.

[d] p-Value for individual predicor (TDF/PI/TDF and PI).

* Significant (p < 0.05) values are in bold.