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Relationships between physical activity and bone density in people living with HIV: Results from the SATURN-HIV Study

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Abstract

We conducted a cross-sectional secondary analysis of baseline data from the SATURN-HIV study ($N = 147$; 78% male, 68% Black, median body mass index [BMI] = 26.72 kg/m², 13% with osteopenia, HIV-1 RNA < 1,000 copies/mL, stable antiretroviral therapy [ART]) to explore the relationship between physical activity (PA) and bone mineral density (BMD). We measured self-reported minutes of PA and BMD in the overall sample and subgroups based on national recommendations (≥ 150 minutes/week). 41 (28%) participants met recommended PA levels. Higher intensity PA was associated with higher BMD at the total hip ($r = 0.27$, $p = 0.09$; $n = 41$; 28%) and lumbar spine ($r = 0.32$, $p < 0.05$), and predicted higher BMD at the hip ($p < 0.01$; controlling for age, BMI, ART). Lumbar spine BMD did not retain significance in the regression model. Moderate-to-high intensity PA could prevent or mitigate excessive bone loss in PLWH.

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Keywords

bone; exercise; HIV; osteoporosis; physical activity

By 2015, 50% of the estimated 1.2 million people living with HIV (PLWH) in the United States were 50 years of age or older (Centers for Disease Control and Prevention, 2015), primarily due to the efficacy of combination antiretroviral therapy (ART). Accompanying this progress was the emergence of a high rate of co-morbidities frequently associated with aging (Guaraldi et al., 2011; Samji et al., 2013), including low bone mineral density (BMD), its more severe form of osteoporosis, and, ultimately, bone fractures (Carr et al., 2015; Castronuovo, Pinzone, Moreno, Cacopardo, & Nunnari, 2015; Hileman, Eckard, & McComsey, 2015; Shiau, Arpadi, & Yin, 2015). While pharmacologic treatments for low BMD are effective, they are not void of adverse events and do not address lifestyle and behavioral factors that contribute to bone loss in PLWH (Cotter & Mallon, 2012). Little is known about the impact of physical activity on BMD and bone loss in PLWH. The purpose of our study was to explore the relationships between physical activity and BMD in a sample of PLWH in the United States.

Skeletal health is maintained across the lifespan through bone remodeling, in which mature or weakened bone is removed by osteoclasts (bone dissolving cells) and replaced with healthy bone tissue by osteoblasts (bone forming cells; McComsey et al., 2010; Rothman & Bessesen, 2012; Shiau et al., 2015). The balance between osteoclastic and osteoblastic activity is mediated by signaling hormones and cytokines that regulate the body's calcium uptake and maintain the integrity of the skeleton (Shiau et al., 2015). Following the point of peak bone mass (typically in young adulthood; National Institute of Arthritis and Musculoskeletal and Skin Diseases [NIAMS], 2015), osteoblastic activity decreases, leading to progressive bone loss as a consequence of aging (Shiau et al., 2015). Accelerated, sometimes pathological, bone loss can occur in individuals with traditional risk factors (e.g., low BMI, menopause, malnutrition; Bolland, Grey, Gamble, & Reid, 2007; Cortés, Yin, & Reame, 2015), behavioral risk factors (e.g., smoking, heavy alcohol consumption, sedentary lifestyle; Emaus, Wilsgaard, & Ahmed, 2014; Goh, Lai, Tan, & Ponnampalavanar, 2017), chronic disease (e.g., HIV, HBV, non-Hodgkin lymphoma, cervical cancer; Shiau et al., 2015), or a combination of the above. When osteoblastic activity is diminished and osteoclastic activity is unregulated, individuals lose bone and are at risk for low BMD (osteopenia) or its more severe form of osteoporosis (Castronuovo et al., 2015; Hileman et al., 2015; Lima et al., 2011; Shiau et al., 2015). This can lead, in time, to painful, and potentially disabling, fractures (Johansson et al., 2014; Mazzotta et al., 2015; Sharma et al., 2015; Yin & Falutz, 2016).

PLWH lose bone at an accelerated rate compared to individuals not living with HIV (Carr et al., 2015; Hileman et al., 2015; Shiau et al., 2015). Although no specific mechanism linking HIV to bone loss has been identified, the cause is likely multifactorial and includes an interplay between factors related to HIV infection and HIV treatment, as well as traditional and behavioral risk factors (Carr et al., 2015; Hileman et al., 2015; Shiau et al., 2015). Soluble HIV-specific proteins (e.g., transactivator of transcription [tat], the transactivating

protein *Rev*, negative regulatory factor [nef]; Beaupere et al., 2015; Chew, Chew, Li, & Lim, 2014), and the chronically inflamed environment created by HIV infection (Brown et al., 2013; Castronuovo et al., 2015; Hileman, Labbato, Storer, Tangpricha, & McComsey, 2014; Shiau et al., 2015) have been hypothesized to dysregulate the process of bone remodeling. They contribute to increased osteoclastic activity with simultaneous suppression of osteoblastic activity. Furthermore, certain HIV medications (e.g., tenofovir, atazanovir; Aukrust et al., 1999; Bonnet et al., 2013; Brown et al., 2009; Brown et al., 2015; Brown, Ross, Storer, Labbato, & McComsey, 2011; Duvivier et al., 2009; Grant et al., 2013; Grund et al., 2009) have been linked to decreased BMD, particularly in the first 2 years after initiating HIV treatment. Compounding bone loss related to HIV and HIV treatment, PLWH have higher incidences of traditional and behavioral risk factors that have or may be linked to bone loss, including low BMI (Buchberg, Gritz, Kypriotakis, Arduino, & Vidrine, 2016), smoking (Lifson & Lando, 2012), and alcohol use (Perazzo & Webel, 2016).

Sedentary lifestyle and behaviors have also been linked to bone loss (Wilsgaard et al., 2009), and PLWH may be at increased risk due to common HIV-associated symptoms (e.g., sleep disturbance, depressive symptoms, fatigue). Conversely, physical activity is associated with improved bone health, even in populations at high risk for bone loss. In the general population, regular physical activity is recommended to achieve optimal bone health (National Osteoporosis Foundation, 2016). Research on the impact of physical activity on bone health in PLWH has been limited; a few studies with small samples have investigated the relationship, but results suggested that regular and consistent moderate-intensity aerobic (Bonato et al., 2012) and resistance (Bonato et al., 2012; Santos et al., 2015) exercise improved bone health and/or prevented bone loss in PLWH (Vecchi et al., 2012). However, a consensus in recent research found that additional well-powered and rigorous research was needed to examine relationships between physical activity and its impact on BMD (Bonato et al., 2012; Fillipas, Cherry, Cicuttini, Smirneos, & Holland, 2015; Santos et al., 2015; Vecchi et al., 2012).

We conducted a secondary analysis of data from the Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV (SATURN-HIV) study to examine the relationship between physical activity and BMD in a sample of adult PLWH. We tested the following hypothesis: PLWH who engaged in recommended levels of physical activity would have higher BMD than individuals who reported lower levels of physical activity.

Methods

Study Overview and Sample

The SATURN-HIV study was a 96-week, randomized, placebo-controlled trial examining the effect of rosuvastatin on cardiometabolic and bone health in PLWH (Eckard, Jiang, Debanne, Funderburg, & McComsey, 2014). Main inclusion criteria for participants were: (a) at least 18 years of age, (b) confirmed HIV-1 infection and on stable ART for at least 3 months with cumulative ART duration of at least 6 months, (c) HIV-1 RNA lower than 1,000 copies/mL, (d) fasting LDL-cholesterol (LDL-C) not higher than 130 mg/dL, (e) triglyceride no higher than 500 mg/dL, and (f) evidence of either heightened CD8+ T-cell activation (% CD8+ T cells that expressed CD38+ and HLA-DR+ of 19%) or levels of high-sensitivity

C-reactive protein (hs-CRP) of at least 2 mg/L. Exclusion criteria for the trial were: (a) history of coronary disease or diabetes, (b) pregnant or lactating, or (c) an active infectious or inflammatory condition other than HIV. Randomization was stratified by protease inhibitor use and by the presence or absence of osteopenia and coronary calcifications. Physical activity and BMD were assessed in all participants. The data presented here were from the baseline visit, in which we assessed physical activity and BMD cross-sectionally prior to the introduction of the rosuvastatin intervention to avoid confounding explanations for changes in BMD. Post hoc power analysis using G*Power indicated that the sample size used in this analysis ($N = 147$) achieved a power of 0.98 assuming a moderate correlation effect size (0.30).

Ethical Approval

The SATURN-HIV study received approval by the institutional review board of University Hospitals Case Medical Center (Cleveland, Ohio), and all participants signed written informed consent. This analysis included secondary analysis of de-identified data from the original study.

Instruments and Measures

Bone mineral density—BMD measurements were collected with dual-energy X-ray absorptiometry (DEXA) at the lumbar (L1-L4) spine and left hip at study entry. All DEXA scans were performed at a single site (University Hospitals Cleveland Medical Center) using a Hologic QDR-4500A (Hologic Inc, Bedford, MA, USA). The scans were assessed with a dedicated densitometer by trained DEXA technologists. Measurement included DEXA-generated BMD values (g/cm^2), and t and z scores.

Physical activity—Physical activity was assessed using the National Institute of Allergy and Infectious Disease AIDS Clinical Trials Group (ACTG) Physical Activity Assessment (McComsey et al., 2007). The measure included 27 physical activities, and study participants were asked to self-report whether they had engaged in each activity in the previous 2 weeks, and the duration of their engagement in each activity. For our analysis, we created three exercise variables based on exercise intensity, which included (a) moderate intensity physical activity (walking, yoga); (b) moderate-to-high intensity physical activity (jogging/running, hiking, dancing, calisthenics, biking); and (c) a total exercise variable (Dirajlal-Fargo et al., 2016). To determine whether participants met current American Heart Association (AHA, 2016) recommendations for weekly physical activity (150 minutes of moderate intensity activity per week; Eckel et al., 2013), we summed the total number of minutes reported for duration of activity in each category during a 2-week timespan and divided by 2 to determine weekly physical activity levels for each participant. Finally, we created a dichotomized categorical variable to classify participants based on whether they met current physical activity recommendations (≥ 150 minutes per week) or did not (< 150 minutes per week; Dirajlal-Fargo et al., 2016).

Assessment of potential confounders—Potential confounding variables (age, BMI, current protease inhibitor and tenofovir use) were collected via participant demographic

questionnaires, anthropometric measures, and data abstracted from participant medical records.

Statistical Analysis

Our objective was to explore the relationships between physical activity and BMD among PLWH. We first checked data quality by running a frequency distribution of variables. To examine demographic characteristics, we calculated frequencies (n , %) for categorical variables and summary statistics (mean, standard deviation) for continuous variables. We used Spearman rank correlations to examine associations between physical activity and BMD. At baseline, we compared individuals who met and did not meet AHA physical activity recommendations, using Mann-Whitney U test or t -test for continuous variables and chi-square test for categorical variables. We checked the distribution of outcome variables and the skewed variable was transformed to zero skewness by applying Box-Cox transformation in order to perform regression analyses. Finally, we used a forward selection procedure in step-wise regression (Field, 2013) to examine the association between BMD and the correlated physical activity variable after adjusting for the covariates of age, BMI, and ART regimen. In this forward selection procedure, we used 0.20 as the probability of a term entering into the model and forced the correlated physical activity variable to retain into the model (Field, 2013). All analyses were conducted using STATA 14.0.

Results

The analysis included data gathered from 147 SATURN-HIV participants during their baseline visits. The sample was predominantly male (78%), an average of 45.4 years of age, and living with HIV for an average of 12 years. The majority of participants (88%) were taking tenofovir and nearly half (49%) were taking protease inhibitors; 13% had DEXA T and Z scores indicative of osteopenia. Demographic and baseline characteristics of the sample are presented in Table 1.

Only 28% of participants in the sample met AHA recommendations for physical activity (150 minutes per week; AHA, 2016). Our two-group analysis of physical activity revealed no significant associations between physical activity engagement and BMD for individuals reporting less than 150 minutes per week of physical activity. Among individuals who reported at least 150 minutes per week of physical activity (Table 2), significant positive correlations between moderate-to-vigorous intensity physical activity and total physical activity were detected. Moderate-to-vigorous physical activity was associated with higher BMD at the total hip ($r = 0.27$; $p = 0.09$) and significantly higher BMD at the lumbar spine ($r = 0.32$; $p < 0.05$). Regression models revealed that moderate-to-vigorous physical activity significantly predicted BMD at the total hip ($p = 0.021$), but not at the lumbar spine ($p = 0.907$). When potential confounders (age, BMI, and ART) were added to the model, moderate-to-vigorous physical activity remained a significant predictor of BMD at the total hip.

Discussion

We investigated the relationship between physical activity and BMD in a group of 147 adults living with HIV for an average of 12 years, on stable ART, and of whom 13% were osteopenic. To our knowledge, this was the first study to explore the impact of free-living physical activity (self-reported activities participants completed in their daily lives; Moy, Mentzer, & Reilly, 2003), and its impact on BMD. We found that, in a group of relatively healthy PLWH participants on stable ART, only 28% reached the recommended levels of weekly physical activity (150 minutes per week). Participants who engaged in this recommended level of physical activity had higher BMD at the total hip compared to those not engaging in recommended levels of physical activity.

Our findings were supported by a growing body of literature that has demonstrated a positive impact of physical activity on bone health (NIAMSD, 2015), including populations at significant risk for bone loss. In the general population, engaging in physical activity is a safe, widely recommended strategy to prevent bone loss after reaching peak bone mass, which occurs typically around the third decade of life (NIAMSD, 2015). During the aging process, physical activity has the potential to prevent bone loss and reduce the risk of fracture (NIAMSD, 2015). Physical activity reduces visceral fat accumulation, subsequently reducing circulating inflammatory mediators (d'Ettorre et al., 2014) that may stimulate osteoclastic activity and inhibit osteoblastic activity (Hileman et al., 2015; Shiau et al., 2015). The anti-inflammatory effects of physical activity have the potential to prevent accelerated bone turnover and prevent bone loss (Hileman et al., 2015; Shiau et al., 2015). Furthermore, in longitudinal studies of populations at high risk for bone loss (e.g., postmenopausal women), consistent participation in physical activity has resulted in favorable changes to BMD and prevention of bone loss (Kemmler, Engelke, & von Stengel, 2016).

Regular physical activity has the potential to produce similar results in PLWH, but this effect cannot be assumed based on data from HIV-uninfected populations. A few small studies have examined relationships between physical activity and BMD in PLWH. Santos et al. (2015) measured changes in BMD in 20 PLWH who participated in a 12-week strength training intervention, resulting in improved BMD at the lumbar spine and femoral neck ($p < 0.05$). Similarly, Bonato et al. (2012) measured changes in BMD in a group of 27 PLWH who participated in a brisk walking and strength training intervention that resulted in improved spinal BMD, as well as femoral BMD in participants who completed the brisk walking intervention. While these investigations were limited by small samples, they produced promising foundational evidence for the efficacy of physical activity interventions to improve BMD and prevent bone loss in PLWH (Bonato et al., 2012; Santos et al., 2015).

Study Limitations

Our study had several limitations. A primary limitation of our analysis was our cross-sectional design, which did not allow an understanding of changes in BMD over time. We examined BMD at the baseline time point for two primary reasons: (a) this pre-treatment time point provided insight into levels of free-living physical activity prior to any

intervention associated with the study, and (b) explanation of changes in BMD would be highly confounded by the introduction of rosuvastatin, which can alter BMD. However, our investigation provided valuable foundation for future work. Prospective, longitudinal studies designed to evaluate the dynamics of bone density in relation to physical activity patterns over time are needed.

Another limitation of our study was the use of a self-reported measure of physical activity. We used the ACTG-adopted physical activity assessment, which, while widely used for PLWH participating in clinical trials, relied on retrospective self-report rather than objective, prospective measurement of physical activity. Self-reported measures of physical activity are subject to participant error due to inability to accurately recall physical activity in the specified time frame as well as over reporting of physical activity due to perceived social desirability. Future studies should use objective measures of physical activity (e.g., accelerometers) in addition to self-report, which will improve the accuracy of findings and provide more insight on dosing of physical activity to improve BMD. Furthermore, a prospective approach would allow scientists to better understand physical activity patterns in PLWH, and to design interventions that could help PLWH integrate weight-bearing/resistance activities that would not only promote overall health, but also reduce the risk of future bone loss. Interventions to increase physical activity in PLWH may be an affordable and, more importantly, sustainable way to promote long-term cardio-metabolic health in PLWH.

Another notable limitation of our analysis was the significant floor effect in the physical activity variable, consequently resulting in a relatively small group of participants who met physical activity recommendations (28% of the sample). Furthermore, our sample was limited by homogeneity, with a majority of participants identifying as African American males. The lack of data on female exercisers and individuals of varying racial and ethnic backgrounds limited the generalizability of our findings. Future exploratory studies could leverage purposive sampling methods to obtain a wider range of physical activity behaviors across a more diverse sample, and provide valuable insight into specific mechanisms that determine active versus sedentary lifestyle behaviors in PLWH.

Conclusion

We found that, in a sample of PLWH, self-report of at least 150 minutes of moderate-to-vigorous intensity physical activity per week was associated with higher BMD at the lumbar spine. However, fewer than 30% of participants reported meeting recommended levels of physical activity. Along with pharmacologic treatment, PLWH could benefit from consistent and long-term engagement in physical activity to prevent bone loss and decrease the risk of fracture. More research aimed at defining effective physical activity interventions tailored to PLWH is needed.

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Key Considerations

- PLWH are at high risk for bone loss due to chronic inflammation, the effects of antiretroviral medications, and behavioral factors such as sedentary lifestyle and substance use.
- Physical activity is a key national health priority with the potential to strengthen bones and prevent bone loss.
- Moderate-to-high-intensity physical activity, when performed for the recommended time of at least 150 minutes per week, was associated with higher bone density at the lumbar spine in PLWH.

Table 1
Participant Characteristics at Baseline (*n* = 147)

Demographic	
	<i>M (SD)</i>
Age at baseline (years)	45.4 (9.9)
Male <i>n</i> (%)	115 (78)
Race <i>n</i> (%)	
• African American	100 (68)
• Caucasian/Hispanic/Other	47 (32)
Body Mass Index (kg/m ²)	28.1 (6.5)
HIV Disease	
Years since HIV diagnosis	12.2 (6.9)
CD4+ T cell count (cells/ul)	639.9 (300)
CD4+ T cell nadir (cells/ul)	200.4 (146.2)
Number of Participants with Viral Suppression; < 75 copies/mL; <i>n</i> (%)	123(83.7)
Currently prescribed Protease Inhibitors; <i>n</i> (%)	72 (49%)
Currently prescribed Tenofovir; <i>n</i> (%)	130 (88%)
Physical Activity	
Number of people engaging in < 150 minutes per week; <i>n</i> (%)	106 (72%)
Number of people engaging in > 150 minutes per week; <i>n</i> (%)	41 (28%)
Average minutes of Moderate Intensity Exercise per week; <i>n</i> (%)	87.6 (305.2)
Average minutes of Moderate to Vigorous Intensity Exercise per week; <i>n</i> (%)	88.5 (325.2)
Average minutes of Total Physical Activity per week; <i>n</i> (%)	186.5 (618.7)

Note. Data presented as mean and frequencies, unless otherwise noted. Data presented as mean (*M*) and standard deviation (*SD*).

Table 2
Baseline Associations Between Physical Activity and Bone Mineral Density

Bone Mineral Density Total Sample (N = 147)				
	Moderate Intensity PA		Moderate to Vigorous Intensity PA	
	r	p-value	r	p-value
Total Hip BMD	-0.021	.80	0.079	.35
Lumbar Spine BMD	-0.141	.09	-0.026	.76
Bone Mineral Density <150 Minutes of Exercise/Week (n = 106)				
	Moderate Intensity PA		Moderate to Vigorous Intensity PA	
	r	p-value	r	p-value
Total Hip BMD	-0.049	0.63	0.052	0.60
Lumbar Spine BMD	-0.077	0.44	-0.052	0.60
Bone Mineral Density ≥150 Minutes of Exercise/Week (n = 41)				
	Moderate Intensity PA		Moderate to Vigorous Intensity PA	
	r	p-value	r	p-value
Total Hip BMD	0.032	0.84	0.272	0.09
Lumbar Spine BMD	-0.194	0.22	0.317	0.04 *

Note.

* statistically significant at ($p < 0.05$);

PA = physical activity; BMD = bone mineral density.

Table 3
Stepwise Regression Model of Bone Mineral Density at Total Hip and Spine

150 Minutes of Exercise per Week			
Total Hip			
Variable	β (SE)	90% CI	<i>p</i> -value
BMI	11.344 (5.481)	(2.096, 20.591)	0.046
On PI	-85.553 (44.097)	(-159.949, -11.157)	0.060
MtoV PA	30.528 (12.629)	(9.222, 51.835)	0.021
Lumbar Spine			
On PI	-0.064 (0.040)	(-0.131, 0.004)	0.120
MtoV PA	-0.001 (0.012)	(-0.021, 0.018)	0.907

Note: BMI = body mass index, expressed as (kg/m²); PI = protease inhibitor, on PI = currently taking regimen containing protease inhibitor (Yes/No); MtoV PA = Moderate to Vigorous Intensity Physical Activity, expressed as minutes/week; re-scaled variable used (re-scaled Variable = Variable/SD).