Clinically Indicated Corticosteroids Do Not Affect Bone Turnover During Immune Restoration of Severely Lymphopenic HIV-Infected Patients

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Abstract

Lymphopenia, corticosteroids, antiretroviral therapy (ART), and inflammation negatively impact bone turnover and decrease bone mineral density, but their combined effect has not been evaluated. We examined the association between corticosteroids on bone turnover markers in severely lymphopenic HIV-infected patients initiating ART. Levels of osteocalcin (bone formation marker) and C-terminal telopeptide (CTX; bone resorption marker) were measured at baseline, weeks 4, 12, and 48 of ART in individuals with severe lymphopenia and opportunistic infection (OI) who received ($n=28$) or did not receive corticosteroids ($n=30$) during the first year of ART, and in a control group with CD4 >200 ($n=15$). Wilcoxon tests were used to compare median values of variables between groups. Correlations between plasma interleukin (IL)-6 and tumor necrosis factor (TNF) levels with bone turnover marker levels were performed using Spearman's coefficient. Individuals given corticosteroids received a median of 21 days at a 35 mg prednisone-equivalent daily dose. Individuals with severe lymphopenia had lower osteocalcin levels at baseline and week 4 and higher CTX levels at ART initiation vs. controls. Bone turnover markers did not differ in severely lymphopenic persons according to corticosteroid receipt. In those with severe lymphopenia, higher IL-6 was associated with higher CTX levels at ART initiation only. HIV-infected patients with severe lymphopenia and OI had lower levels of bone formation and higher levels of bone resorption than those initiating ART at higher CD4. Corticosteroid use, as prescribed during OI, was not associated with bone turnover. In contrast, higher markers of systemic inflammation prior to ART were associated with greater bone resorption.

Introduction

LOW BONE MINERAL DENSITY (BMD) occurs in approximately 50% of HIV-infected individuals.¹ HIV-infected individuals are at a 1.5- to 5-fold increased risk of fragility fractures compared to uninfected individuals.^{2,3} The etiology of bone fragility in HIV is multifactorial with contributions from traditional osteoporosis risk factors, HIV infection and its associated chronic inflammation, and antiretroviral therapy (ART).

A consistent finding across studies is the significant bone loss that occurs during the first year of ART,⁴⁻⁶ which is similar in magnitude to the loss that occurs during early menopause.⁷ The cause of bone loss during early ART is unlikely to be solely a result of a medication effect, because

bone loss occurs with most regimens studied and BMD appears to stabilize after the first year of ART.^{4,8} Additionally, several studies have identified associations between inflammatory and immune abnormalities and bone loss in HIV.⁹⁻¹¹

Dual-energy X-ray absorptiometry (DXA) is routinely used to screen individuals for osteoporosis, with the risk of fracture approximately doubling for each standard deviation reduction in BMD.¹² However, low BMD is only one of several risk factors for fracture. Bone turnover marker (BTM) levels are also an independent risk factor for fracture¹³ and can provide an assessment of bone turnover in shorter time scales than DXA. BTMs indirectly assess bone metabolism, measuring collagen breakdown products and other molecules released from osteoclasts and osteoblasts during bone resorption and formation.

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Corticosteroids have well-described detrimental effects on bone including BMD loss, high bone resorption and low bone formation, fractures, and avascular necrosis.^{14–16} Systemic corticosteroids are frequently used in individuals with severe lymphopenia and active opportunistic infections (OIs) as adjunctive therapy for OI management [e.g., pneumocystis pneumonia (PCP), cerebral toxoplasmosis, and tuberculous meningitis] or for treatment of Immune Reconstitution Inflammatory Syndrome (IRIS). The effect of corticosteroids on bone metabolism in individuals with an active OI has not been studied. Here, we examine the relationship between severe lymphopenia, corticosteroid use, and levels of proinflammatory markers on BTMs in patients initiating ART and specifically address the question of whether corticosteroid use in individuals with severe lymphopenia may be associated with an adverse impact on bone turnover during immune restoration.

Materials and Methods

Subjects

From a prospective study enrolling ART-naïve HIV-infected patients at the NIH Clinical Center between 2007 and 2012 with CD4 counts <100 cells/ μ l (NCT00286767), we selected patients who had an AIDS-defining OI and had achieved and maintained viral suppression by week 48 (i.e., HIV RNA level <50 copies/ml at weeks 24, 36, and 48). We identified 28 patients who received systemic corticosteroids for a clinical indication during the first year of ART. We also identified 30 patients matched by age and CD4 count with an AIDS-defining OI who did not receive corticosteroids. As a control group, we selected patients from another NIH Clinical Center study (NCT00789009) who were enrolled and initiated on HIV therapy during the same era with a pre-ART CD4 count of >200 cells/ μ l, achieved viral suppression, and who did not receive corticosteroids during the first year of ART ($n=15$). All participants provided written informed consent for study participation.

Assays and time points

Using cryopreserved plasma samples from ART initiation and ART weeks 4, 12, and 48, we assessed bone formation with osteocalcin (MSD System, Rockville, MD) and resorption with C-terminal telopeptide (CTX; Immunodiagnostic Systems, Gaithersburg, MD). We also evaluated plasma levels of interleukin (IL)-6 and tumor necrosis factor (TNF) at the same time points using an electrochemiluminescence multiplex assay (MSD System, Rockville, MD).

Statistics

We used descriptive statistics to summarize the study population. To examine associations between severe lymphopenia and corticosteroids and BTMs at each time point, we compared levels of osteocalcin and CTX between those with or without severe lymphopenia and an active OI and also compared levels in those with severe lymphopenia who did or did not receive corticosteroids using the Wilcoxon rank sum test. We evaluated the trajectory of osteocalcin and CTX levels in the entire study cohort and made comparisons between the above groups in change in BTM levels over 48 weeks with the Wilcoxon signed rank test.

We used the Wilcoxon signed rank test to evaluate the trajectory of IL-6 and TNF levels over 48 weeks as well as to make intergroup comparisons of changes over 48 weeks. We determined the correlation between IL-6 and TNF levels with BTMs at each time point in the overall study population, and in those with severe lymphopenia and in the control population using the Spearman's rank correlation coefficient. All analysis testing was two-sided with a type I error of 5%; thus p -values of <0.05 were considered statistically significant with no adjustment for multiple comparisons.

Results

Table 1 displays the baseline characteristics of the 73 study participants. The median age was 34 years (IQR 29, 41); 71% were men. Numerically, more of the control population (vs. those with severe lymphopenia) were categorized as other race, generally mixed race of Hispanic ethnicity (53% vs. 7%). The median baseline CD4 count and viral load in the individuals with severe lymphopenia was 15 cells/ μ l (IQR 6, 34) and 5.1 log₁₀ copies/ml (IQR 4.7, 5.6), respectively. In the control population, the median values were 262 cells/ μ l (IQR 206, 378) and 4.5 log₁₀ copies/ml (4.4, 4.7), respectively. Ninety-six and 26% of the entire cohort initially received tenofovir- and protease inhibitor-containing regimens, respectively. Among the patients with severe lymphopenia, the most common presenting OIs were mycobacterial infections (mostly tuberculosis and MAC) and PCP. Including non-AIDS-defining OIs such as oropharyngeal candidiasis, 86% of the patients with severe lymphopenia presented with multiple OIs. Not surprisingly, PCP was overrepresented in the group of patients with OIs who received corticosteroids for a clinical indication (57%) vs. the group of patients with OIs who did not receive corticosteroids (10%).

Overall, individuals in the entire cohort had a robust response to ART with a median increase in CD4 count of 171 cells/ μ l (IQR 101, 221) and a decrease in viral load of 3.3 log₁₀ copies/ml (IQR 2.9, 3.7) at 48 weeks. The indications for corticosteroid administration were treatment of PCP ($n=13$), IRIS ($n=6$), toxoplasmosis ($n=4$), tuberculosis ($n=2$), VZV vasculitis and transverse myelitis ($n=2$), and tinnitus ($n=1$). The median duration of corticosteroids use was 21 days (IQR 15, 41) at a median daily prednisone-equivalent dose of 35 mg (IQR 25, 53). Corticosteroids were used at various times during the 48 weeks of follow-up with 39% (11/28) of individuals receiving corticosteroids at ART initiation.

Compared to the control population, patients with severe lymphopenia had a lower median level of the bone formation marker osteocalcin at both ART initiation (Table 2; 23.2 vs. 37.9 ng/ml; $p=0.013$) and at week 4 of ART (median 35.8 vs. 51.8 ng/ml; $p=0.017$), but osteocalcin levels were not significantly different between these groups at later time points. Compared to the control population, individuals with severe lymphopenia had a higher median level of the bone resorption marker CTX at ART initiation (Table 3; 0.60 vs. 0.38 ng/ml; $p=0.038$), but this difference was not sustained at later time points.

In the entire study cohort, both osteocalcin and CTX levels increased over 48 weeks of ART ($p<0.001$ for both comparisons). However, there was a greater median increase from ART initiation to ART week 48 in the bone formation marker

TABLE 1. BASELINE CHARACTERISTICS

	Total (n = 73)	OI/CS (n = 28)	OI /no CS (n = 30)	CD4 > 200, no OI/No CS (n = 15)
Age, years (IQR)	34 (29, 41)	34 (30, 45)	33 (29, 41)	33 (28, 39)
Sex				
Male	52/73 (71%)	19/28 (68%)	21/30 (70%)	12/15 (80%)
Female	21/73 (29%)	9/28 (32%)	9/30 (30%)	3/15 (20%)
Race				
Black	36/73 (49%)	15/28 (54%)	15/30 (50%)	6/15 (40%)
White	25/73 (34%)	12/28 (43%)	12/30 (40%)	1/15 (7%)
Other	12/73 (16%)	1/28 (4%)	3/30 (10%)	8/15 (53%)
BMI, kg/m ² (IQR)	24 (21, 26)	22 (20, 25)	25 (22, 26)	24 (22, 25)
CD4 count, cells/ μ l (IQR)	25 (9, 124)	14 (11, 32)	16 (6, 36)	262 (206, 378)
Plasma HIV-RNA, copies/ml (IQR)	5.0 (4.5, 5.4)	5.1 (4.7, 5.7)	5.1 (4.7, 5.6)	4.5 (4.4, 4.7)
TDF-containing ART	70/73 (96%)	27/28 (96%)	28/30 (93%)	15/15 (100%)
PI-containing ART	19/73 (26%)	9/28 (32%)	8/30 (27%)	2/15 (13%)
OI at presentation				
Mycobacteria	21/73 (29%)	7/28 (25%)	14/30 (47%)	N.A.
PCP	19/73 (26%)	16/28 (57%)	3/30 (10%)	
CMV infection	12/73 (16%)	3/28 (11%)	9/30 (30%)	
Toxoplasmosis	7/73 (10%)	4/28 (14%)	3/30 (10%)	
Cryptococcal infection	5/73 (7%)	1/28 (3%)	4/30 (13%)	
Multiple OIs	50/73 (68%)	23/28 (82%)	27/30 (90%)	

Median values are shown with % or interquartile range in parentheses.

OI, opportunistic infection; CS, corticosteroids; BMI, body mass index; IQR, interquartile range; TDF, tenofovir disoproxil fumarate; ART, antiretroviral therapy; PI, protease inhibitor; PCP, pneumocystis pneumonia; CMV, cytomegalovirus.

osteocalcin in individuals with severe lymphopenia vs. the control group (+44.4 vs. +18.3 ng/ml; $p < 0.001$). Additionally, there was a smaller median increase from ART initiation to ART week 48 in the bone resorption marker CTX in those with severe lymphopenia vs. the control group (0.24 vs. 0.41 ng/ml; $p = 0.045$). There was no difference in BTM levels (or change in BTM levels) in those with severe lymphopenia according to corticosteroid receipt at any of the time points evaluated.

Overall, there was a significant decline in both IL-6 and TNF levels from baseline to 48 weeks in the entire study cohort ($p < 0.001$ for both comparisons). There was a greater median decline in IL-6 levels from baseline to 48 weeks in the severely lymphopenic vs. the control patients (−1.94 vs. −0.02 pg/ml; $p < 0.001$; Fig. 1A and B). However, there was no difference in the 48-week decline in TNF levels in severely lymphopenic patients vs. controls (−3.73 vs. −3.37 pg/ml; $p = 0.77$).

In the entire study cohort, we found a positive correlation between IL-6 and CTX levels ($r = 0.38$; $p = 0.001$) and a nonsignificant weak negative correlation between IL-6 and osteocalcin levels ($r = -0.23$; $p = 0.055$) at ART initiation but no suggestion of a relationship between IL-6 and BTM levels at subsequent time points. When we analyzed the individuals with severe lymphopenia and the control population separately, there remained a strong relationship between IL-6 and CTX levels at baseline in patients with severe lymphopenia ($r = 0.39$; $p = 0.004$; Fig. 1F) but not in the control population ($r = 0.02$; $p = 0.95$; Fig. 1E). There was no relationship at any time point between TNF levels and BTMs (data not shown).

Discussion

In this analysis of bone turnover markers in 73 individuals over the first 48 weeks of ART, individuals with severe lymphopenia and an active OI (compared to those with a

TABLE 2. MEDIAN OSTEOCALCIN LEVEL BY GROUP, ng/ml (IQR)

	Severe lymphopenia		Controls	p-value
	Corticosteroids	No corticosteroids		
ART week 0	23.2 (13.7, 36.7)		37.9 (25.3, 54.2)	0.013
	22.9 (12.7, 31.3)	23.4 (17.1, 39.5)		0.16
ART week 4	35.8 (25.3, 48.7)		51.8 (44.4, 66.9)	0.017
	37.7 (30.9, 48.7)	32.5 (18.4, 45.5)		0.45
ART week 12	62.0 (41.6, 81.0)		61.2 (35.1, 67.8)	0.38
	66.1 (48.2, 73.1)	48.1 (38.9, 79.1)		0.93
ART week 48	67.0 (49.9, 100.8)		54.9 (45.2, 88.6)	0.12
	71.3 (52.3, 98.9)	65.7 (49.1, 103.5)		0.83

TABLE 3. MEDIAN C-TERMINAL TELEPEPTIDE LEVEL BY GROUP, ng/ml (IQR)

	<i>Severe lymphopenia</i>		<i>Controls</i>	<i>p-value</i>
	<i>Corticosteroids</i>	<i>No corticosteroids</i>		
ART week 0	0.60 (0.34, 0.88)		0.38 (0.26, 0.52)	0.04
	0.52 (0.35, 0.96)	0.64 (0.26, 0.83)		0.64
ART week 4	0.73 (0.61, 1.07)		0.64 (0.45, 0.92)	0.12
	0.74 (0.62, 0.94)	0.69 (0.61, 1.18)		0.85
ART week 12	0.92 (0.67, 1.06)		0.79 (0.53, 1.21)	0.44
	0.94 (0.62, 1.06)	0.85 (0.68, 1.05)		0.82
ART week 48	0.76 (0.60, 1.14)		0.81 (0.56, 1.19)	0.12
	0.77 (0.62, 1.22)	0.76 (0.59, 1.05)		0.66

relatively more intact immune system at ART initiation) had lower levels of the bone formation marker osteocalcin at ART initiation and at 4 weeks after ART initiation and higher levels of the bone resorption marker C-terminal telopeptide at baseline. There was no additional adverse impact of corticosteroid use, however, on these bone turnover marker levels. Finally, an association between IL-6 levels and bone turnover marker levels at ART initiation was observed, tying inflammation to bone turnover.

This is the first analysis to our knowledge that has looked at bone turnover markers longitudinally specifically in individuals with severe lymphopenia initiating ART. Our findings provide additional support for the known relationship between low CD4 and poor bone health. Previous findings have shown that low baseline CD4 count is predictive of subsequent bone loss and the development of osteopenia after ART initiation^{1,8} and that low CD4 is associated with a greater risk of fragility fractures.¹⁷ Similar to others, we

FIG. 1. Trajectory of plasma cytokine levels and their relationship to bone turnover markers at antiretroviral therapy (ART) initiation. Trajectory over 48 weeks of ART of interleukin (IL)-6 and tumor necrosis factor (TNF) levels in severely neutropenic (A) and in control patients (B). Relationship between IL-6 with osteocalcin-1 (C, D) and C-terminal telopeptide (CTX) (E, F) in severely neutropenic and control patients.

found that bone turnover markers generally increase with ART,^{6,18} and in our study, change in bone turnover marker levels was not affected by the receipt of corticosteroids. Reassuringly, soon after initiation of ART, bone turnover marker levels in individuals with severe lymphopenia are similar to those who initiated HIV at an earlier disease stage, consistent with the well-known return to health effect of ART.

Corticosteroids have well-established adverse effects on the bone with a clear relationship seen between corticosteroid use and fracture in the general population.^{19,20} In HIV-infected individuals, corticosteroid use also has been shown to be associated with fracture risk,¹⁷ but the duration of corticosteroid use in the latter study was not characterized. In our study cohort, corticosteroids were used for a relative short period of time (median 3 weeks), and we did not see any difference in bone turnover markers at any of the time points in individuals with severe lymphopenia who did or did not receive corticosteroids. In uninfected individuals, even a short duration of corticosteroids (i.e., <1 month) has been shown to negatively affect bone formation and bone resorption.²¹ Our data suggest that there may not be an additive negative effect of limited-course corticosteroids on bone health in individuals with advanced immunosuppression in the setting of ART initiation. Importantly, the indication of corticosteroid use was to temper infection-related inflammation, suggesting the possibility that the negative effect of corticosteroids on bone health might have been offset by the overall decrease in inflammation.

Chronic immune activation and proinflammatory cytokines appear to play a role in the pathogenesis of bone density loss in HIV-infected individuals.^{22,23} Osteoclast activity is stimulated by proinflammatory cytokines such as TNF and IL-6,^{24,25} both of which are increased in HIV-infected patients.^{26–28} Other studies have shown a relationship between both increased IL-6 levels and activated CD4 and CD8 T cells and bone loss or osteoporosis.^{9,10} Interestingly, while we found an association between higher IL-6 levels and lower bone formation markers and higher bone resorption markers at ART initiation, this association did not hold at later time points and was seen only in the severely lymphopenic patients, suggesting that while bone loss in untreated HIV is related to inflammation, the bone loss that occurs with therapy is likely multifactorial and may be due to other factors such as ART and traditional osteoporotic risk factors.

There are several limitations to our study that deserve highlighting. We assessed bone turnover markers and not change in BMD by DXA. BTM levels have been associated with BMD change in HIV-infected patients²⁹ and predict fracture in the general population.¹³ Corticosteroid dose, duration, and timing in our study were variable and it is important to note that participants were not on corticosteroids at all time points measured. However, this may make our results more generalizable as the indication of corticosteroids was clinical and dictated by standard of care. Our study was not randomized and the study population was small, which did not allow for clinical events (fractures) or secondary analyses to control for differences in baseline characteristics between groups. However, it is unlikely that differences in baseline characteristics between groups could explain our findings, because if that were the case differences between groups would be expected to persist throughout the 48-week study

and not be limited to early ART, as we saw with our data. Additionally, almost all individuals in the study received tenofovir, so the differential impact of various antiretrovirals could not be determined. Finally, because this was an analysis with multiple comparisons, marginally significant associations should be interpreted cautiously.

In conclusion, we found at initiation and during early ART, participants with advanced HIV had lower levels of bone formation and higher levels of bone resorption, but this did not persist later during the first year of ART. Corticosteroids, as prescribed for a limited course during an OI, did not significantly impact bone turnover. A higher IL-6 level at ART initiation, but not at later time points, was associated with lower levels of bone formation and higher levels of bone resorption. Our results support the hypothesis that initiation of ART at a higher CD4 count, in addition to many other benefits, may reduce the burden of osteoporosis and fragility fractures among HIV-infected patients.

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Author Disclosure Statement

No competing financial interests exist.

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