Assessment of Associations between Markers of Renal Function and Bone Mineral Density in HIV-positive and HIV-negative Subjects

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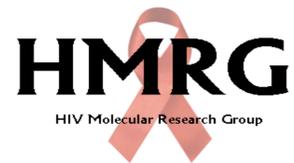
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Introduction

HIV infected individuals have higher prevalence of renal disease and low bone mineral density (BMD) compared with HIV uninfected controls [1-3]. Renal dysfunction may induce bone damage as a secondary effect, but the relationship between these pathologies remains poorly understood.

Aims

We aimed to determine relationships between specific markers of renal function and bone parameters.

Methods

Cross-sectional analysis of the HIV UPBEAT cohort, comparing HIV-positive and HIV-negative subjects from similar demographic backgrounds.

We collected demographic and clinical history, including regional dual X-ray absorptiometry (DXA) from the UPBEAT clinical database.

Renal/ bone profile and bone turnover markers (BTMs) from fasting blood samples and protein, creatinine, phosphate and glucose from fresh frozen urine samples.

We further estimated the renal function using:
• eGFR-MDRD4: Normal >90mL/min/1.73m^2
• Protein/creatinine ratio (P/Cr): Normal <15 mg/mmol
• Retinol binding protein/Creatinine ratio: (RBP/Cr)
  Normal <130 µg/g if age<50 and <172 µg/g if age>50
• Maximal reabsorption capacity of phosphate (TmP/GFR): Normal >0.8 mmol/L

Statistical analysis:
• Descriptive statistics: median, interquartile range (IQR) and absolute (percentage frequencies)
• Between-groups differences: Mann-Whitney/Student's t test and Chi-squared tests (Fisher's exact test)
• Relationships between renal markers and bone parameters: Spearman correlation methods
• Independent associations between markers of renal function and bone parameters: univariate/multivariable linear regression models adjusted for demographic / life style factors and BMI (model 1), HIV-status (model 2) and laboratory variables including BTMs (model 3).

Results

A total of 419 subjects with available urine sample at baseline were included in the analysis.

Patient characteristics are detailed in Table 1.

Within the HIV-positive group, the median (IQR) time since HIV diagnosis was 5 (2-8) years, median (IQR) CD4+ T-cell count was 476 (350-653) (cells/mm^3), 89% were currently on ART of whom 78% had undetectable RNA-HIV (<50 copies/mL).

Table 1. Baseline characteristics

N=419 N(%)	HIV-positives (N=169)	HIV-negatives (N=250)	p
Male	103 (60.9)	111 (44.4)	0.001
African ethnicity	61 (36.7)	64 (25.6)	0.01
Age (years)*	39 (33-47)	42 (35-49)	0.02
BMI (kg/m^2)*	26 (23-29)	27 (25-30)	0.005
HCV-coinfection	15 (8.8)	3 (1.2)	<0.0001
Hypertension	31 (25)	43 (21)	0.41
Diabetes	2 (1.2)	3 (1.2)	0.35
Current smoker	68 (40.2)	38 (15.2)	<0.0001
Current alcohol	98 (57.9)	189 (75.6)	<0.0001

* Median (IQR).
BMI: body mass index; HCV: hepatitis C virus.

Results

▪ **Renal and Bone function**

Average, serum renal and bone parameters were within normal range, with no differences in prevalence of abnormal parameters between HIV-positive and HIV-negative subjects.

However, there were higher P/Cr and RBP/Cr ratios in the HIV-positive group compared with the control group (all p<0.001) (Table 2).

The HIV-positive group showed a significantly higher bone turnover and lower BMD compared with the control group (all p<0,001), in agreement with previous results from the entire UPBEAT cohort[3].

▪ **Associations between renal and bone parameters**

Higher RBP/Cr ratio significantly correlated with lower LS-, FH-, and TH-BMD (r=-0.183, r=-0.204, r=-0.193, all p<0.001). Patients with abnormal RBP/Cr had significantly lower BMD at each site (Figure 1). Similar associations were found between P/Cr ratio and BMD at the 3 sites (r=0.173, r=-0.163, r=-0.171, respectively).

Table 2. Urinary parameters of renal function

N=419	HIV-positives (N=169)	HIV-negatives (N=250)	p
Protein			
P/Cr (mg/mmol)	8.6 (6.7-14.2)	6.3 (5.0-9.5)	<0.0001
P/Cr >15	28 (17)	8 (3)	<0.0001
RBP/Cr (µg/g)	105.29 (68.1-192.4)	71.51 (50.7-108.4)	<0.0001
Abnormal RBP/Cr*	62 (37)	26 (11)	<0.0001
Phosphate			
TmP/GFR (mmol/L)	1.02 (0.8-1.3)	1.01 (0.9-1.2)	0.23
Abnormal TmP/GFR	24 (15)	26 (11)	0.36
Glucose			
Uglucose>1 (mmol/L)	2 (1.2)	5 (2)	0.70

*Abnormal RBP/Cr: RBP/Cr >130 µg/g if age<50 and >172 µg/g if age>50.

Figure 1. BMD at each site according to RBP/Cr and P/Cr values
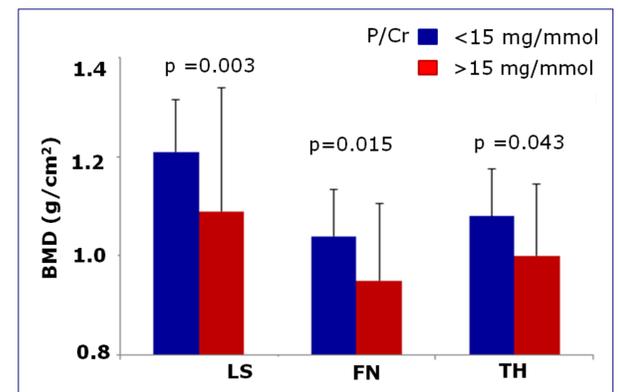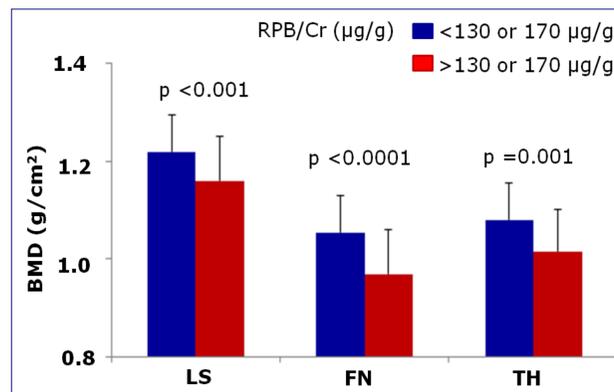
On univariate testing, RBP/Cr, P/Cr and HIV status were associated with reduced BMD at FN, LS and TH (all p<0.0001). In addition, African ethnicity, current smoking, third education level and lower BMI were all associated with lower BMD at the 3 anatomical sites.

After adjustment for demographic /life-style factors and BMI (model 1, Table 3), RBP/Cr but not P/Cr was independently associated with lower BMD at FN, LS and TH with the association remaining robust with further adjustment for HIV-status (model 2, Table 3). Further adjustment for laboratory parameters (parathyroid hormone and alkaline phosphatase) and BTMs (model 3, Table 3) minimally abrogated the effect of RBP/Cr on BMD whereas the effect of HIV on BMD was largely reduced.

Table 3. Parameter estimates (coefficients B) and 95% confidence interval (95%CI) from multivariate linear regression models exploring relationships of RBP/Cr, P/Cr and HIV infection with BMD at FN, LS and TH.

BMD_FN (g/cm^2)	Model 1 B	95% CI	p	Model 2 B	95% CI	p	Model 3 B	95% CI	p
RBP/Cr (per20 µg/g↑)	-0.006	-0.011, -0.003	0.003	-0.005	-0.008, -0.001	0.01	-0.004	-0.007, -0.001	0.04
P/Cr (per5mg/mmol↑)	-0.002	-0.005, 0.001	0.13	-	-	-	-	-	-
HIV-positive status	-0.073	-0.107, -0.040	<0.0001	-0.063	-0.098, -0.029	<0.0001	-0.015	-0.053, 0.023	0.30
BMD_LS (g/cm^2)	**B**	**95% CI**	**p**	**B**	**95% CI**	**p**	**B**	**95% CI**	**p**
RBP/Cr (per20 µg/g↑)	-0.006	-0.010, -0.002	0.001	-0.006	-0.010, -0.002	0.006	-0.005	-0.009, -0.001	0.02
P/Cr (per5mg/mmol↑)	-0.003	-0.006, 0.001	0.12	-	-	-	-	-	-
HIV-positive status	-0.074	-0.112, -0.035	<0.0001	-0.064	-0.103, -0.026	0.001	-0.021	-0.066, 0.023	0.34
BMD_TH (g/cm^2)	**B**	**95% CI**	**p**	**B**	**95% CI**	**p**	**B**	**95% CI**	**p**
RBP/Cr (per20 µg/g↑)	-0.005	-0.009, -0.001	0.010	-0.004	-0.007, 0.000	0.048	-0.003	-0.006, 0.001	0.12
P/Cr (per5mg/mmol↑)	-0.001	-0.004, 0.001	0.35	-	-	-	-	-	-
HIV-positive status	-0.084	-0.116, -0.052	<0.0001	-0.081	-0.114, -0.047	<0.0001	-0.035	-0.073, 0.002	0.06

Discussion

The excretion of protein in urine was the only parameter significantly different between HIV-positive and HIV-negative subjects.

Tubular proteinuria, measured by RBP/Cr, but not total proteinuria, is associated with reduced BMD at the 3 anatomical sites. This association persists even correcting for by HIV infection and BTMs.

Further studies are needed to understand the mechanisms underlying this association and the contribution of specific HIV-related factors to alterations in renal and bone parameters.

References and Acknowledgements

1.Shcouten J. et al.CID 2014; 2. Brown TT, Qaqish RB. AIDS 2006; 3. Cotter AG et al., AIDS 2014