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Effects of renal tubular dysfunction on bone in HIV positive patients

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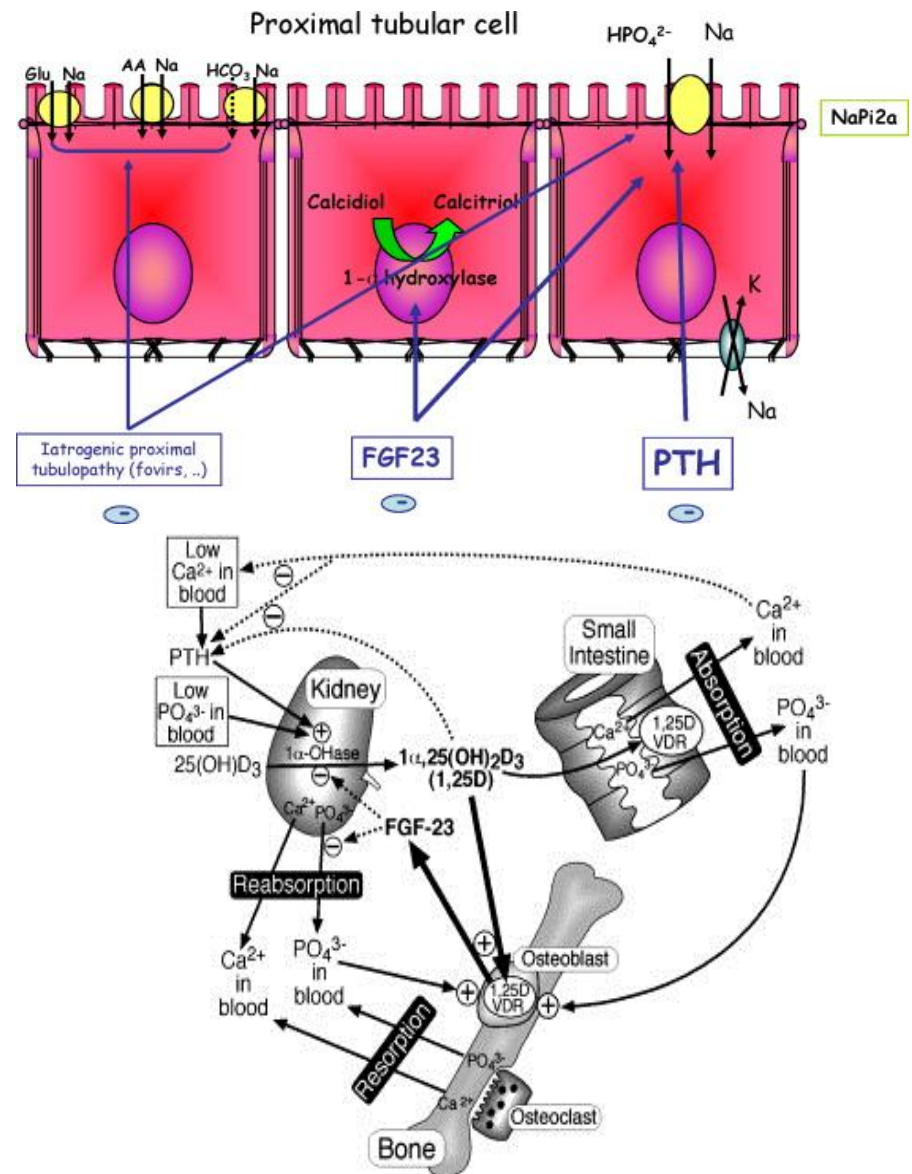
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Renal tubular dysfunction and HIV

- Renal tubular dysfunction prevalence rates vary widely (12-81%)
- Renal tubular dysfunction is associated with combination antiretroviral therapy (cART)
 - Tenofovir in combination with boosted PIs increases the risk
- Other risk factors
 - increasing age
 - genetic polymorphisms in the tubular transporter proteins MRP-2, MRP-4 and MRP-7

Renal tubular dysfunction and HIV

- Renal tubular dysfunction causes impaired reabsorption of phosphate in the proximal tubule
- In its most extreme form, renal tubular dysfunction causes Fanconi syndrome
- Fanconi syndrome results in calcium and phosphate dysregulation and osteomalacia
- BUT... does sub-clinical renal tubular dysfunction affect bone mineral function?



Urinary retinol-binding protein (RBP)

- Low-molecular weight proteins (e.g. RBP) are freely filtered through the glomerulus and reabsorbed in the proximal tubule
- Increased excretion of these 'tubular proteins' provides a sensitive indicator of tubular dysfunction
- RBP is a sensitive and specific functional marker of renal tubular dysfunction
- Urinary RBP is expressed as a creatinine ratio (RBPCR)

Aims

- To measure urinary RBPCR and evaluate its association with age, ethnicity, renal function, HIV factors and cART exposure
- To explore the association of RBPCR with bone turnover and bone mineral density (BMD)

Methods

- Cross-sectional cohort of HIV-infected men randomly selected from a UK outpatient centre
- Clinic database: demographic factors, HIV factors including mode of acquisition and cART exposure
- Fasting blood and urine to measure:
 - estimated glomerular filtration rate (eGFR)
 - fractional excretion of phosphate (FEPO₄)
 - RBPCR (normal range <2.93 µg/mmol)
 - Bone resorption: C-terminal telopeptide crosslinks (CTX)
 - Bone formation: N-terminal propeptide of type I collagen (P1NP)
- Absolute BMD measured at femoral neck using Hologic QDR 2000 dual energy xray absorptiometry

Demographics

	Total N=438
Age years mean (SD)	47 (10)
White ethnicity n (%)	412 (94)
MSM n (%)	408 (93)
Years since HIV diagnosis median (IQR)	9.3 (4.8, 15)
Prior AIDS defining illness n (%)	10 (2)
cART n (%)	
On treatment at recruitment	387 (88)
VL <40	376 (97)
Current TDF	293 (67)
Current PI	184 (42)

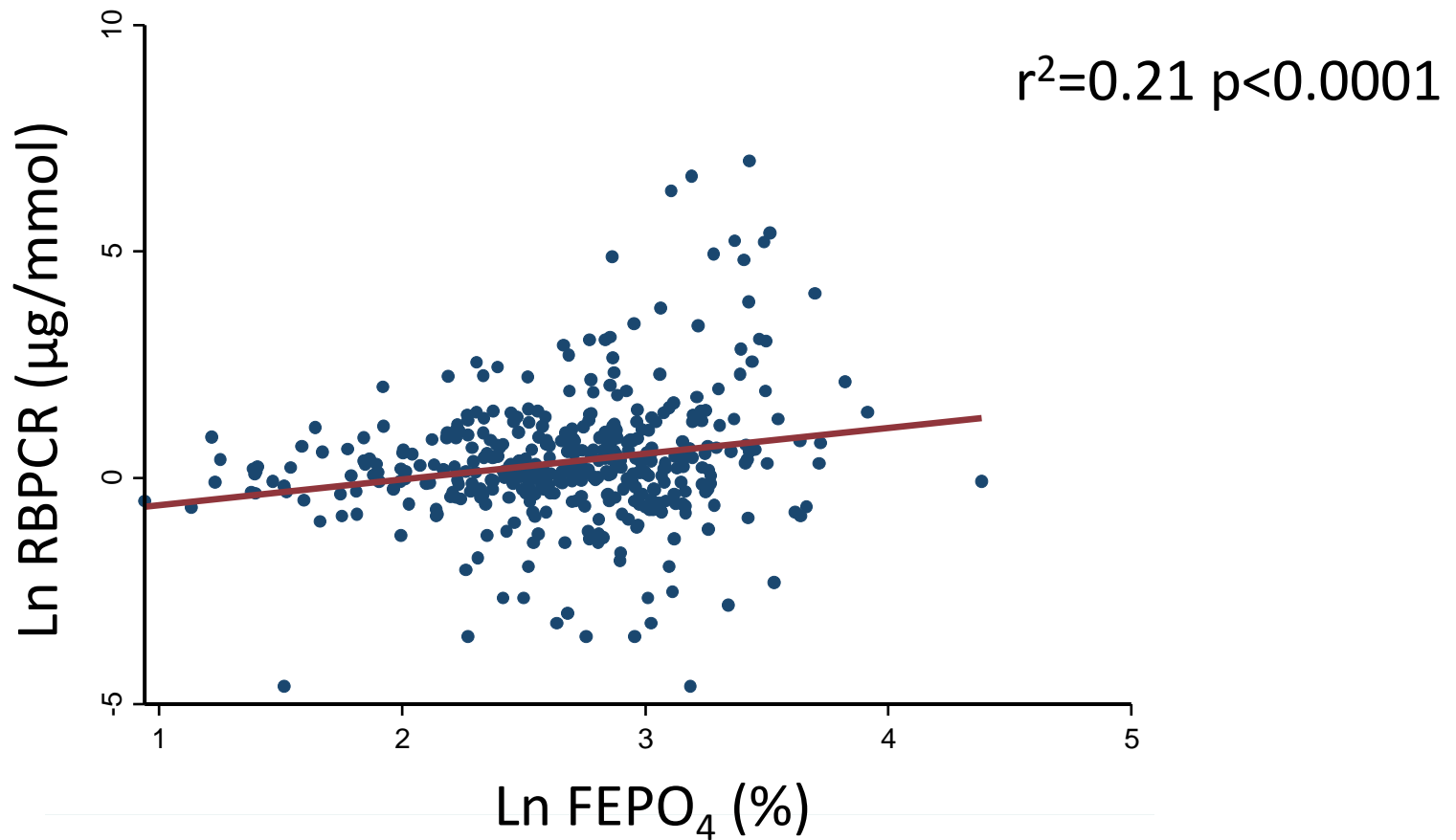
MSM: men who have sex with men, AIDS: acquired immune deficiency disease, cART: combination antiretroviral therapy, VL: viral load copies/ml, TDF: tenofovir, PI: protease inhibitor

Renal function

	N=438
eGFR (CKD-Epi) mean (SD)	94 (17)
eGFR n (%)	
>90	261 (60)
60-90	163 (37)
<60	14 (3)
RBPCR n (%)	
>2.93 (>ULN)	87 (20)
>14.65 (>5x ULN)	23 (5)
Phosphate wasting n (%)	
FEPO ₄ >10 and serum PO ₄ <0.8	118 (27)

eGFR: estimated glomerular filtration rate ml/min/1.73cm², CKD-Epi: chronic kidney disease epidemiology collaboration, RBP: urine retinol binding protein (µg/mmol), RBPCR: urine retinol binding protein (ug/L) expressed as a ratio with urine creatinine (µmol/L), ULN: upper limit of normal, FEPO₄: fractional excretion phosphate (%), PO₄: serum phosphate mmol/L

Correlation between RBPCR and phosphate



Associations with RBPCR >2.93 (n=87)

	Crude OR (95%CI)	P-value	Adjusted OR*	P-value
Age per 5yr ↑	1.19 (1.06, 1.34)	0.004	0.96 (0.82, 1.12)	0.60
CD4 nadir	0.98 (0.97, 1.00)	0.02	0.99 (0.98, 1.01)	0.42
Viral load (log₁₀)	0.70 (0.51, 0.97)	0.03	1.18 (0.60, 2.29)	0.63
On treatment	6.90 (1.62, 29.4)	0.002	3.74 (0.52, 27.0)	0.19
Current TDF	2.64 (1.26, 5.54)	0.008	1.26 (0.67, 2.36)	0.48
Current PI	1.95 (1.20, 3.14)	0.006	1.37 (0.81, 2.33)	0.24
eGFR per 10ml/min ↓	1.43 (1.25,1.64)	<0.00001	1.40 (1.18, 1.66)	<0.0001

CD4: CD4 positive cell count, VL: viral load copies/ml, TDF: tenofovir, PI: protease inhibitor, eGFR: estimated glomerular filtration rate, RBPCR: urine retinol binding protein (µg/L) expressed as a ratio with urine creatinine (mmol/L), PCR: urine protein creatinine ratio

*Adjusted for age, nadir CD4 cell count, current viral load, current cART use, current TDF use, current PI use, CKD-Epi derived eGFR

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Associations with RBPCR >14.65 (n=23)

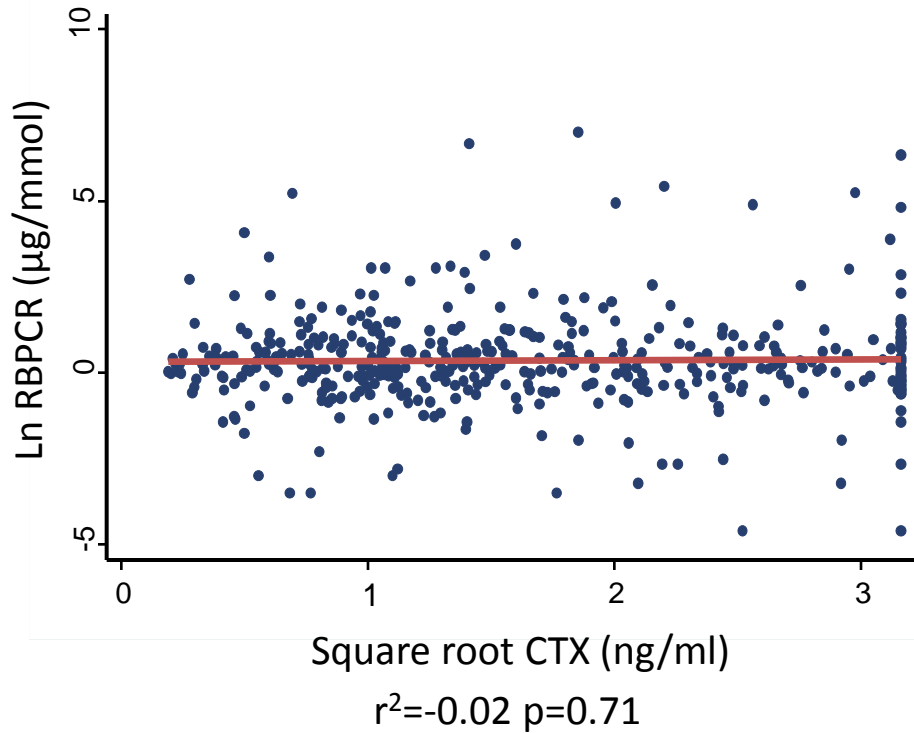
	Crude OR (95%CI)	P-value	Adjusted OR*	P-value
Age per 5yr ↑	1.35 (1.09, 1.66)	0.005	0.96 (0.71, 1.29)	0.78
CD4 nadir	0.97 (0.94, 1.00)	0.04	0.98 (0.94, 1.01)	0.22
Viral load (log₁₀)	0.63 (0.35, 1.12)	0.11	-	-
On treatment	-	-	-	-
Current TDF	2.44 (0.81, 7.36)	0.10	-	-
Current PI/r	2.73 (1.12, 6.62)	0.02	1.67 (0.61, 4.57)	0.32
eGFR per 10ml/min ↓	2.02 (1.58, 2.57)	<0.00001	1.84 (1.34, 2.52)	<0.0001

CD4: CD4 positive cell count, VL: viral load copies/ml, TDF: tenofovir, PI: protease inhibitor, eGFR: estimated glomerular filtration rate, RBPCR: urine retinol binding protein (µg/L) expressed as a ratio with urine creatinine (mmol/L), PCR: urine protein creatinine ratio

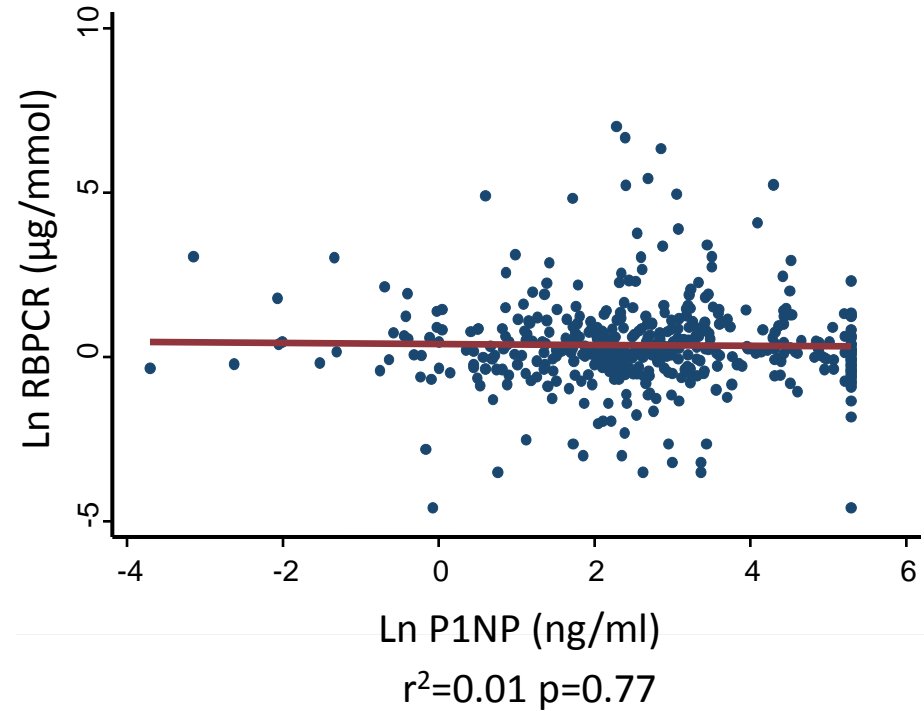
*Adjusted for age, nadir CD4 cell count, current PI use, CKD-Epi derived eGFR

Correlations between RBPCR and bone turnover

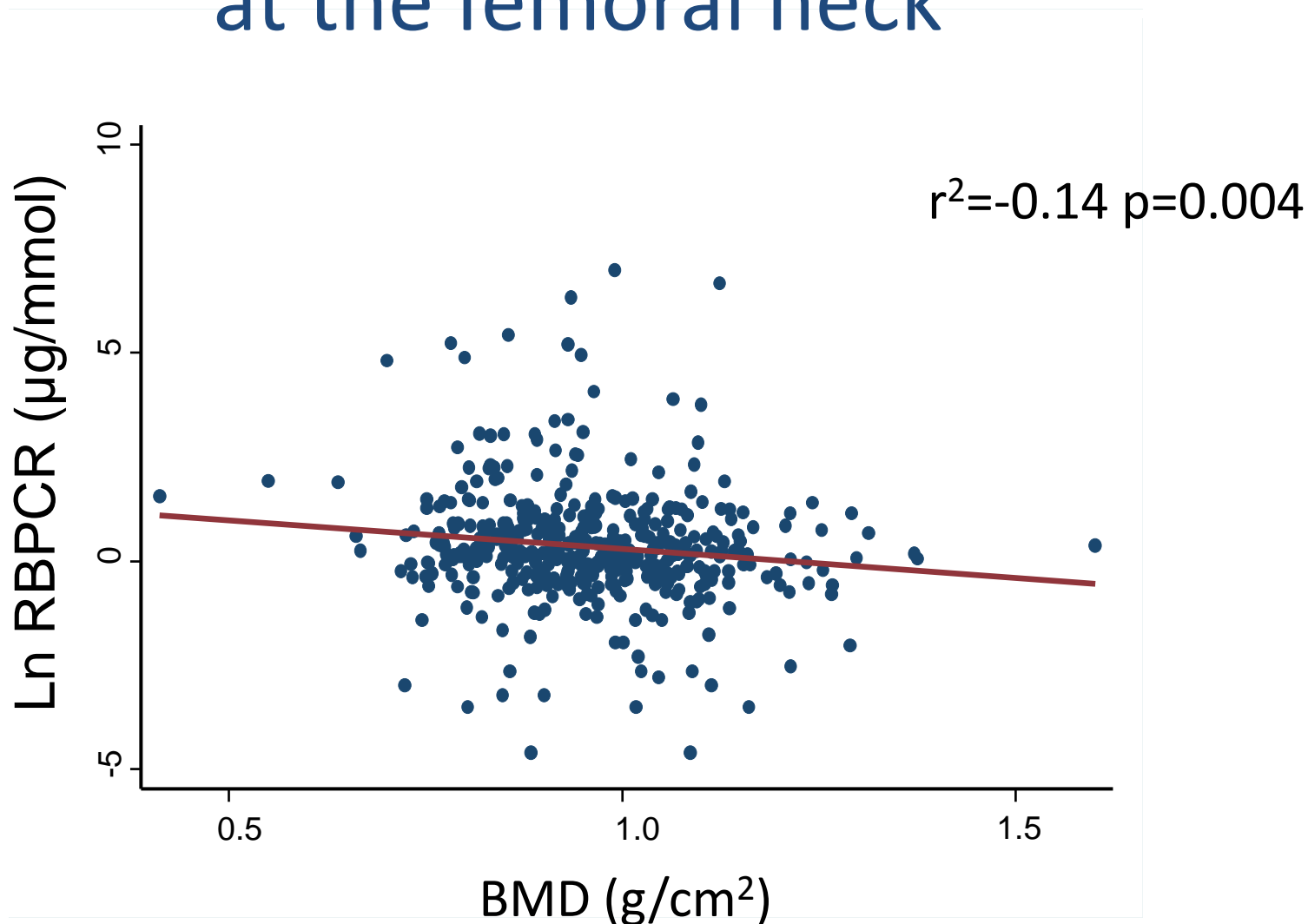
Correlation between RBPCR and CTX (bone resorption)



Correlation between RBPCR and P1NP (bone formation)



Correlation between RBPCR and BMD at the femoral neck



Relationship between RBPCR and femoral neck BMD

	Crude Co-efficient	(95% Confidence Interval)	P-value	Adjusted co-efficient [#]	(95% Confidence Interval)	P-value
Ln RBPCR	-0.013	(-0.022, -0.004)	0.004	-0.009	(-0.017,-0.0002)	0.05
RBPCR						
<2.93						
2.93-14.65	-0.028	(-0.063, 0.008)	0.132	-0.022	(-0.060, 0.016)	0.26
>14.65	-0.052	(-0.110, 0.005)	0.072	-0.046	(-0.100, 0.007)	0.09

RBPCR: urine retinol binding protein ($\mu\text{g/L}$) expressed as a ratio with urine creatinine ($\mu\text{mol/L}$), BMD: bone mineral density (g/cm^2)

[#]Adjusted for age, ethnicity, HIV transmission risk, years since HIV diagnosis, CD4 nadir, viral load, years on treatment, antiretroviral regimen, eGFR, body mass index, smoking status, steroid exposure, low testosterone and sedentary lifestyle

Relationship between RBPCR and femoral neck BMD

	Crude Co-efficient	(95% Confidence Interval)	P-value	Adjusted co-efficient#	(95% Confidence Interval)	P-value
Ln RBPCR	-0.013	(-0.022, -0.004)	0.004	-0.009	(-0.017,-0.0002)	0.05
RBPCR						
<2.93						
2.93-14.65	-0.028	(-0.063, 0.008)	0.132	-0.022	(-0.060, 0.016)	0.26
>14.65	-0.052	(-0.110, 0.005)	0.072	-0.046	(-0.100, 0.007)	0.09

RBPCR: urine retinol binding protein ($\mu\text{g/L}$) expressed as a ratio with urine creatinine ($\mu\text{mol/L}$), BMD: bone mineral density (g/cm^2)

#Adjusted for age, ethnicity, HIV transmission risk, years since HIV diagnosis, CD4 nadir, viral load, years on treatment, antiretroviral regimen, eGFR, body mass index, smoking status, steroid exposure, low testosterone and sedentary lifestyle

Summary

- 20% of HIV positive men had RBP-defined renal tubular dysfunction
- 5% had severe RBP-defined renal tubular dysfunction (RBPCR >5 x ULN)
- Renal tubular dysfunction was associated with lower eGFR and higher FEPO₄, but not with CD4 cell count, HIV RNA, or antiretroviral drugs
- RBPCR did not correlate with markers of bone turnover
- There was a borderline association between RBPCR and femoral neck BMD

Conclusions

- In this cross-sectional study, no association between renal tubular dysfunction and bone turnover
- Borderline association between renal tubular dysfunction and BMD at the femoral neck
- Clinical significance for patients with renal tubular dysfunction and its impact on bone is still unknown
- Longitudinal study is ongoing

Acknowledgements

- BHIVA Research Awards (2011)
- Fowzia Ibrahim (KCL)
- Maggie Cole (CIRU)

The logo of the British HIV Association (BHIVA) is a circular emblem with a complex, geometric pattern of lines and dots, resembling a stylized sun or a network. It is positioned behind the main title text.

British HIV Association
BHIVA

A light blue map of the United Kingdom is centered in the background. A red circular marker is placed on the map, indicating the location of Manchester in the north-western region of England.

**19th Annual Conference of the
British HIV Association (BHIVA)**

16–19 April 2013

#BHIVA2013

Manchester Central Convention Complex