

Associations between Endothelial Dysfunction and Proteinuria, Albuminuria, and Renal Function in Stable, HIV-infected Patients



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Abstract

Background: Renal disease is a strong and independent predictor of cardiovascular disease (CVD) in the general population. Systemic endothelial dysfunction may be the link between CVD and proteinuria, albuminuria, and reduced renal function. In a small pilot study, however, we found that these markers of renal disease were not associated with endothelial dysfunction in non-diabetic and non-hypertensive HIV-infected patients. We sought to confirm and extend these findings in a larger study.

Methods: A cross-sectional analysis of 104 (73% male, 37% non-Hispanic Black) non-diabetic, non-hypertensive, HIV-infected patients without known CVD and who either did not require antiretroviral therapy (ART) or were on a stable ART was performed. The associations between flow mediated dilation (FMD) of the brachial artery, a measure of systemic endothelial function, and spot urine protein to creatinine ratio (P/Cr), albumin to creatinine ratio (A/Cr), and renal function (estimated as both creatinine clearance (CrCl) by the Cockcroft-Gault formula and as glomerular filtration rate (GFR) by the simplified MDRD formula) were determined using Spearman Correlation Coefficients, Wilcoxon tests, and multivariable linear regression models.

Results: The median (IQR) age and CD4 cell counts were 40 (34, 46) years and 416 (271, 645)/mm³, respectively. 47% were receiving ART and 86% of the entire cohort had HIV-1 RNA levels <400copies/mL. The median (IQR) FMD (%), nitroglycerin-mediated dilation (%), P/Cr (g/g), A/Cr (g/g), CrCl (ml/min), and GFR (ml/min/1.73m²) were 4.4(2.9, 7.3), 15.9(12.6, 23.2), 0.073(0.053, 0.10), 0.0037(0.0023, 0.006), 118 (96, 139), and 102 (90, 119), respectively. In univariate analyses, FMD was significantly and negatively correlated with P/Cr [$r=-0.26$, $p=0.01$] and A/Cr [$r=-0.20$, $p=0.05$] but not with CrCl or GFR. In multivariable analysis, however, P/Cr and A/Cr were no longer associated with FMD after controlling for baseline diameter, age, sex, and race. Similar results were found in the subgroups not receiving ART or in those with HIV-1 RNA <400copies/mL.

Conclusions: This larger study confirms that systemic endothelial dysfunction may not independently contribute to nephropathy in stable HIV-infected patients without diabetes, hypertension, or known CVD.

Introduction I

- Renal disease is a strong and independent predictor of cardiovascular disease (CVD) in the general population.
- Systemic endothelial dysfunction may be the link between CVD and proteinuria, albuminuria, and reduced renal function.
- HIV infection, independent of ARV effects and other co-morbidities, is associated with both impaired endothelial function and with more severe nephropathy. Thus, it is reasonable to hypothesize that renal disease markers in the HIV-infected population would be associated with endothelial dysfunction.

Introduction II

- However, in a small pilot study (Gupta et al. JAIDS, 2007) we found that neither proteinuria nor albuminuria were associated with endothelial dysfunction in non-diabetic and non-hypertensive HIV-infected patients.
- We sought to confirm and extend these findings in a larger study.

Methods

- Cross-sectional analysis of 104 HIV-infected patients (all non-diabetic, non-hypertensive, not receiving lipid-lowering therapy, no known CVD, no current OI) either not on ART or on stable ART.
- Flow-mediated dilation (FMD) of the brachial artery used to measure *in vivo* endothelial function
- Spot albumin and protein to creatinine ratios. (A/Cr, P/Cr) measured as estimates of albuminuria and proteinuria, respectively.
- Renal function estimated using both creatinine clearance (CrCl) using the Cockcroft-Gault equation and with glomerular filtration rate (GFR) using the simplified MDRD equation.
- Univariable relationships between FMD and A/Cr, P/Cr, CrCl, and GFR examined using Spearman Correlation Coefficients and Wilcoxon Rank Sum tests.
- Multivariable, linear regression models were then constructed to adjust for potential confounding variables.

Results I

SUBJECT CHARACTERISTICS*	
N=104	
Variable	Value
Female (n, %)	28 (27)
Non-Hispanic Black (n, %)	38 (37)
Age (yrs)	40 (34, 46)
CD4 count (cells/ μ L)	416 (271, 645)
Receiving ART (n, %)	49 (47)
HIV-1 RNA <400copies/mL (n, %)	48 (46)
Current smokers (n, %)	63 (61)
Systolic blood pressure, mmHg	116 (108, 126)
Diastolic blood pressure, mmHg	71 (65, 80)
HOMA-IR	2.29 (1.78, 3.21)
Triglycerides (mg/dL)	104 (79, 166)
Total cholesterol (mg/dL)	166 (147, 196)
LDL-C (mg/dL)	97 (82, 121)
HDL-C (mg/dL)	42 (33, 52)
Baseline diameter, mm	4.0 (3.4, 4.5)
FMD (%)	5.4 (2.9, 7.3)
NTGMD (%)	15.9 (12.6, 23.2)
P/Cr (g/g)	0.073 (0.053, 0.10)
>0.2 (n, %)	10 (10)
A/Cr (mg/g)	3.7 (2.3, 8.0)
>30 (n, %)	11 (11)
CrCl (mL/min)	118 (96, 139)
<60 (n, %)	3 (3)
GFR (mL/min/1.73 ²)	102 (90, 119)
<60 (n, %)	3 (3)

*Values presented as median (interquartile range) except where specified.

Results II

- **UNIVARIABLE CORRELATES OF FMD**
- Significant correlates of higher FMD included:
 - Female vs. male (7.5 \pm 6.4% vs. 5.1 \pm 4.2%; $P=0.01$)
 - Baseline diameter ($r = -0.40$; $P<0.0001$)
 - HDL-C ($r = 0.22$; $P=0.03$)
 - P/Cr ($r = -0.26$; $P=0.01$)
 - A/Cr ($r = -0.20$; $P=0.05$)
- A/Cr > 30mg/g and P/Cr > 0.2g/g were not associated with FMD.
- CrCl and GFR were not associated with FMD.
- Age, race, CD4 cell count, current receipt of ART, HIV-1 viral load, lipids, blood pressure, HOMA-IR, and smoking status were not associated with FMD.
- **MULTIVARIABLE ANALYSIS**
- After adjustment for age, race, sex, and baseline diameter, P/Cr and A/Cr were no longer significantly associated with FMD.
- Similar results were found when the analysis was restricted to only those currently receiving ART or to those with an HIV-1 viral load \geq 400 copies/mL.

Discussion

- Frequencies of HIV-related proteinuria, albuminuria, and impaired renal function were similar to those reported in other studies.
- CrCl and GFR were not correlated with endothelial function.
- Albuminuria and proteinuria were significantly, albeit weakly, correlated with endothelial function in univariable analysis.
- Albuminuria and proteinuria were not associated with endothelial function after adjustment for baseline diameter, age, sex, and race.
- These same relationships held for the subgroups of participants not currently receiving ART or with HIV-1 RNA levels \geq 400copies/mL.
- HIV-related endothelial dysfunction does not appear to contribute to nephropathy in patients without HTN, DM, or known CVD.
- If HIV-related endothelial dysfunction contributes to future CV events, then conventional renal disease markers may not identify those at higher risk of atherosclerotic disease due to HIV infection.

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