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Proteinuria and Endothelial Dysfunction in Stable HIV-Infected Patients: A Pilot Study

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There is an increasingly recognized need to identify HIV-infected patients at higher risk for cardiovascular events using easily obtainable and inexpensive markers. One such marker may be proteinuria, which predicts future cardiovascular events in the general population.[1] Proteinuria has historically been associated with HIV-associated nephropathy (HIVAN), which typically affects those of African descent.[2] However, recent investigations have documented that HIV-related proteinuria (and albuminuria, which may be a more specific marker of glomerular function) is commonly found in both blacks and whites and even in those without diabetes or marked hypertension.[3]

The development of systemic endothelial dysfunction is an early step in the progression of atherosclerosis and has been suggested as the mechanistic link between the presence of proteinuria and the development of cardiovascular disease.[4] Both HIV itself[5] and its therapies[6] have been associated with endothelial dysfunction. We, therefore, hypothesized that proteinuria may be associated with endothelial dysfunction in HIV-infected patients, including those without other traditional cardiovascular risk factors.

We performed a pilot, cross-sectional study evaluating flow-mediated dilation (FMD) as a measure of endothelial function in prospectively enrolled, HIV-infected subjects with and without persistent proteinuria (defined as two consecutive spot urine protein-to-creatinine ratios obtained during screening visits 4–8 weeks apart of at least 25.0mg/mmol each and without pyuria). Exclusion criteria included age less than 18 years, known vascular or renal disease, serum creatinine > 124μmol/L, hemoglobin < 80g/L, temperature > 38.0°C, or suspected active infection of any kind (besides HIV) at the time of each screening and study visit. In order to reduce confounding from traditional risk factors for both proteinuria and endothelial dysfunction, subjects were excluded if they had uncontrolled hypertension or known diabetes mellitus. Subjects then underwent standardized endothelial function testing[7] using a single technician within four weeks of the second screening urine test. All

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measurements were made by a single investigator (S.K.G.) who was blinded to the subjects' proteinuria status. This study was approved by the Clarian Health (Indiana University School of Medicine) Institutional Review Board. Written, informed consent was obtained prospectively from all subjects.

The characteristics of the 34 subjects (28 non-proteinuric, 6 proteinuric) enrolled into this study are shown in Table 1. The mean FMD and NTGMD in the overall group were 5.1% and 17.2%, respectively. There were no significant differences between groups in terms of baseline diameters, flow measurements, or other endothelial function parameters. Interestingly, multivariable linear regression analysis of the entire study cohort suggested that the strongest predictor of greater FMD was the use of lopinavir/ritonavir [N=8; beta-coefficient 3.089 (standard error 1.608); p=0.06]. Neither proteinuria nor albuminuria was associated with FMD in either univariable or multivariable analyses using the entire cohort. In contrast to most forms of proteinuric nephropathies, albuminuria was generally not the major component of the total proteinuria observed in this cohort, accounting for only a small proportion (median 8%; IQR 5%–16%) of the total proteinuria observed.

Similar to other investigations,[5] we found in the current study low FMD results with intact nitroglycerin-mediated dilation. Contrary to our expectations, however, we did not observe any associations between markers of renal impairment and endothelial dysfunction in this group. Endothelial function associated with HIV has been attributed to both HIV infection itself or with its therapies, especially protease inhibitors. For example, Stein et al[6] enrolled subjects primarily receiving indinavir, which was commonly used at the time that study was performed. Moreover, this agent may directly impair endothelial function.[8] No subject in this current study, however, was using indinavir. Interestingly, we noted a possible benefit to the receipt of the lopinavir/ritonavir which is consistent with a recent report[9] of improved endothelial function in healthy HIV-uninfected men receiving this agent. These results suggest that there may be marked heterogeneity in regards to the effects on endothelial function within the protease inhibitor class of antiretrovirals.

Although proteinuria[10] and albuminuria[11] have been associated with impaired FMD in other populations, we could not confirm this relationship in stable HIV-infected patients without diabetes, uncontrolled hypertension, or advanced chronic kidney disease. It is unlikely that misclassification bias accounted for the lack of association between proteinuria and FMD in this study as proteinuria was strictly defined as persistent elevations of protein/creatinine ratios without evidence of pyuria over the 1–2 month screening period. Although we cannot exclude the possibility that the negative relationships found between proteinuria and albuminuria with FMD was due to the small sample size in this study, we identified no trends relating proteinuria or albuminuria with FMD in either categorical or continuous variable analyses. In fact, FMD appeared was nominally higher in the proteinuric subjects, although this did not reach statistical significance.

Albuminuria accounted for only a small portion of the total proteinuria in this study, which corroborates another recent investigation that suggested that tubular proteins may be the predominant components of total proteinuria in HIV-infected patients without diabetes or hypertension.[12] In contrast, albuminuria does appear to be the major component of proteinuria in HIV-infected patients with diabetes or marked hypertension.[13] This suggests that, in the absence of conditions classically associated with glomerular impairment and endothelial dysfunction, treated HIV infection may result primarily in tubular proteinuria. This finding may explain why total proteinuria does not seem to be a reliable identifier of more impaired FMD in the current study. However, we cannot exclude the possibility that proteinuria may be significantly associated with endothelial dysfunction in HIV-infected subjects with diabetes or hypertension.

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Table 1.

Characteristics of the study cohort[a]

Characteristic	Non-proteinuric (N=28)	Proteinuric (N=6)
Age, yrs	45 (23, 62)	49 (39, 59)
Male sex, n (%)	19 (68)	5 (83)
Black race, n (%)	11 (39)	3 (50)
Smoker, %[b]	17 (61)	3 (50)
Systolic blood pressure[c], mmHg	111 (97, 145)	119 (108, 133)
Body mass index, kg/m²	27 (19, 40)	27 (19, 34)
Waist to hip ratio	1.00 (0.87, 1.75)	0.97 (0.91, 1.02)
CD4, cells/μL	498 (12, 1534)	535 (12, 1021)
HIV-1 RNA level < 400 copies/mL[d], n (%)	23 (82)	2 (33)
Urine protein/creatinine, mg/mmol	9.0 (3.4, 15.9)	48.6 (27.1, 109.7)
Urine albumin/creatinine, mg/mmol	0.5 (0.1, 5.6)	12.8 (1.3, 29.8)
Creatinine clearance, mL/min[e]	119 (72, 202)	98 (65, 164)
Hepatitis C Ab positive, n (%)	3 (12)	1 (17)
Serum glucose, mmol/L	5.2 (3.9, 6.6)	4.9 (4.2, 6.1)
Serum triglyceride, mmol/L	1.8 (0.7, 6.5)	1.5 (0.9, 1.8)
Serum total cholesterol, mmol/L	4.5 (3.0, 8.1)	4.4 (3.8, 5.9)
Serum HDL-C, mmol/L	0.8 (0.4, 1.4)	1.5 (0.7, 2.6)
Serum LDL-C, mmol/L	1.8 (0.9, 4.3)	2.0 (0.5, 3.9)
Flow-mediated dilation, %	4.8 (−4.2, 12.9)	7.8 (0.4, 10.5)

[a] Values presented as median (range) except where noted. All laboratories were obtained after a 12 hour fast prior to endothelial function measurements. HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol.

[b] Past or current tobacco use.

[c] Mean of three values obtained at screening and main study visits.

[d] p=0.03 for the difference between groups.

[e] Estimated using Cockcroft-Gault equation.