Albuminuria Is Associated with Elevated Acute Phase Reactants and Proinflammatory Markers in HIV-Infected Patients Receiving Suppressive Combination Antiretroviral Therapy

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Abstract

Albuminuria among HIV-infected individuals has been found to be associated with cardiovascular disease (CVD) and mortality. Inflammation has been associated with albuminuria. The pathophysiology of albuminuria in HIV-infected individuals is poorly understood. We investigated the association of albuminuria with inflammatory biomarkers among HIV-infected individuals on combination antiretroviral therapy (cART). This is a cross-sectional analysis of participants enrolled in the Hawaii Aging with HIV-Cardiovascular Cohort. Plasma inflammatory biomarkers were assessed using the Milliplex Human Cardiovascular disease multiplex assays. A random urine sample was collected for albumin measurement. Albuminuria was defined as urine albumin-to-creatinine ratio of ≥ 30 mg/g. Framingham risk score was calculated and divided into three classes. Simple and multivariable logistic regression analyses were utilized to assess the correlation between plasma inflammatory biomarkers and albuminuria and were adjusted for Framingham risk category. Among 111 HIV-infected patients [median (IQR) age of 52 (46–57) years, 86% male, median (IQR) CD4 count of 489 (341–638) cells/mm³, 85% with HIV RNA <50 copies/ml], 18 subjects (16.2%) had moderately increased albuminuria (albuminuria range between 30 and 300 mg/g) and 2 subjects (1.8%) had severely increased albuminuria (albuminuria more than 300 mg/g). In multivariable logistic models, sE-selectin, sVCAM-1, CRP, SAA, and SAP remained significantly associated with albuminuria after adjustment of CVD risk factors. This study showed an association between inflammation and albuminuria independent of previously reported risk factors for albuminuria in HIV-infected subjects who were on combination antiretroviral therapy (cART). Chronic inflammation despite potent antiretroviral treatment may contribute to higher rates of albuminuria among HIV-infected patients.

Introduction

MICROALBUMINURIA OR A preferred term, moderately increased albuminuria, is more prevalent in HIV-infected individuals (4–20%) compared to the general population (2%).^{1–9} Albuminuria has been shown to be associated with cardiovascular disease (CVD), subclinical atherosclerosis including greater carotid intima media thickness and coronary artery calcium, heart failure, and higher all-cause and AIDS-related mortality.^{3,4,10} The pathophysiological mechanism of albuminuria in HIV-infected individuals is still

unresolved. In the past, albuminuria and kidney diseases in HIV-infected individuals were commonly caused by HIV-associated nephropathy and HIV immune complex kidney diseases. However, in the era of highly active antiretroviral therapy, the causes have shifted to comorbid diseases such as hypertension and diabetes mellitus as well as side effects of antiretroviral therapy including renal tubular cell toxicity from tenofovir.^{3,11}

Albuminuria was shown to be associated with inflammatory biomarkers in various conditions in HIV-seronegative individuals including type 2 diabetes, hypertension, inflammatory

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bowel disease, rheumatoid arthritis, non-Hodgkin's lymphoma, as well as patients with cancer and febrile neutropenia.^{12–19} Thus, inflammation may play an important role in the pathogenesis of albuminuria. Studies linking inflammation and albuminuria in HIV-infected individuals are limited. One study from Baekken *et al.* showed the correlation between albuminuria and increased serum β_2 -microglobulin, a marker of cellular activation and HIV immunoactivity.⁶ Another study has shown the correlation with serum neutrophil gelatinase-associated lipocalin (NGAL), an inflammatory marker produced by neutrophils and other cells.²⁰

In the present study we hypothesized that in HIV-infected individuals whose disease was well controlled with combination antiretroviral therapy (cART), albuminuria is associated with chronic inflammation independent of traditional risk factors and toxicity from antiretroviral therapy. We chose to study whether a relationship existed between biomarkers of CVD and albuminuria. Commercially available panels of CVD-associated biomarkers were selected for testing. Inflammatory markers including endothelial cell adhesion molecules (E-selectin, VCAM-1, ICAM), proinflammatory cytokines [interleukin (IL)-1b, IL-6, tumor necrosis factor (TNF)- α], acute phase reactants (CRP, SAA, SAP), chemotactic factors [IL-8, monocyte chemoattractant protein-1 (MCP-1)], and other factors including tissue plasminogen activator inhibitor-1 (tPAI-1), matrix metalloproteinase-9 (MMP-9), myeloperoxidase (MPO), IL-10, vascular endothelial growth factor (VEGF), and interferon (IFN)- γ were assessed.

Materials and Methods

Study population

A cross-sectional study utilized entry data from the Hawaii Aging with HIV-Cardiovascular Study, a 5-year natural history longitudinal cohort study designed to investigate the role of oxidative stress and inflammation on the pathogenesis of CVD in HIV-infected individuals. Details on enrollment and clinical characteristics are published elsewhere.²¹ Briefly, the study enrolled 158 HIV-infected adults age ≥ 40 years old, living in the state of Hawaii. Inclusion criteria included documented HIV-positive status and having been on combination antiretroviral therapy for at least 6 months. IRB approval was obtained from the University of Hawaii, and all subjects provided informed consent prior to entry into the study.

Inflammatory biomarker parameters

Plasma was forwarded to Blood Systems Research Institute, San Francisco, CA (S. Keating and P. Norris) for multiplex biomarker testing. Plasma samples were assayed for soluble inflammatory mediators using antibody-coated beads in a high sensitivity Milliplex assay (Human CVD panels A, B, and C, EMD Millipore, Billerica, MA). Standard curves and samples were tested in duplicate. Samples were acquired on a Labscan 200 analyzer (Luminex, Austin, TX) using Bio-Plex manager software (Bio-Rad, Hercules, CA).

Clinical parameters

General medical and HIV-specific history and medication history including antiretroviral medications were obtained. Clinical parameters assessed included height, weight, and

blood pressure. Blood parameters assessed included fasting lipids, glucose, and insulin as well as results from an oral glucose tolerance test. HIV-specific laboratory measurements included CD4 count and plasma HIV-RNA viral levels.

Framingham Risk Score (FRS) was calculated based on a model composed of age, gender, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, treatment of hypertension, and any cigarette smoking in the past month using the National Cholesterol Education Program website (<http://hp2010.nhlbi.nih.net/atp/iii/calculator.asp>).²² Subjects were classified into the following FRS risk categories: low risk (FRS < 10%), intermediate risk (FRS from 10% to 19.99%), and high risk (FRS $\geq 20\%$). Subjects with diabetes (as a CVD equivalent) or clinical CVD (history of myocardial infarction, angina, coronary disease-related cardiac surgery, or ischemic stroke) were automatically classified under high risk. Clinical CVD was adjudicated by two physician-researchers (C.M.S and D.C.C.).

Urine albumin

The level of urine albumin was determined by immunoturbidimetric assay using a Roche/Hitachi MODULAR P analyzer by a commercial College of American Pathologist (CAP)-certified laboratory (Diagnostic Laboratory Inc). Albuminuria was defined as a urine albumin-to-creatinine ratio (ACR) of more than or equal to 30 mg/g, as assessed from random urine collection. Moderately increased albuminuria was defined as a urine ACR between 30 and 300 mg/g; and severely increased albuminuria, a preferred term for macroalbuminuria was defined as urine ACR more than 300 mg/g.⁹

Statistical analyses

Albuminuria was dichotomized as an ACR of more than or equal to 30 mg/g versus less than 30 mg/g.

Differences in clinical and laboratory characteristics between subjects without and with albuminuria were compared using the nonparametric Wilcoxon rank test for continuous variables and chi-squared test for categorical variables.

Simple and multivariable logistic regression analyses were utilized to assess the association between the presence of albuminuria as the dependent variable and plasma biomarkers, and Framingham risk category as independent variables. Log-transformed plasma inflammatory biomarkers with a *p*-value less than 0.1 in simple logistic regression were selected for examination in separate multivariable logistic regression models, adjusting for Framingham risk category. A two sided probability of *p*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS statistical program (SPSS Statistics 21, Armonk, NY).

Results

Of the 158 subjects in the parent cohort, 111 subjects had both urine albumin and inflammatory markers available for this analysis. Demographics and clinical characteristics are summarized in Table 1. Study subjects were predominantly male (86%) and white (56%), with a median age of 52 years. Among the 111 evaluable subjects, 10% had diabetes mellitus and almost 39% had hypertension. Eighty-five percent of subjects had undetectable plasma HIV RNA, and in those with detectable viremia the range was from 50 to 6,280

TABLE 1. COMPARISON OF HIV-SEROPOSITIVE PARTICIPANTS WITH AND WITHOUT ALBUMINURIA

Characteristics	Total (n = 111)	Patients with albuminuria (n = 20)	Patients without albuminuria (n = 91)	p-value
Age, years	52 (46,57)	57 (49,61.5)	51 (46,56)	0.01
Male, n (%)	95 (86)	18 (90)	77 (84.6)	0.73
Race, n (%)				
White	62 (56)	13 (65)	49 (53.8)	0.36
Other races	49 (44)	7 (35)	42 (46.2)	
BMI, kg/m ²	25.8 (23.7, 28)	25.9 (22.4, 28.4)	25.8 (23.9, 27.9)	0.86
Diabetes mellitus, n (%)	11 (10)	4 (20)	7 (7.7)	0.11
Hypertension, n (%)	43 (38.7)	12 (60)	31 (34.1)	0.03
Framingham Risk Score, %	6 (3, 15)	20 (9, 20)	5 (2, 11)	<0.001
Framingham Risk Score category				<0.001
Low risk	67 (60)	6 (30)	61 (67)	
Intermediate risk	22 (20)	3 (15)	19 (21)	
High risk	22 (20)	11 (55)	11 (12)	
Creatinine, mg/dl	1.0 (0.9, 1.1)	1.05 (0.9, 1.2)	1.0 (0.9, 1.1)	0.15
GFR, ml/min				
CKD-EPI	85.4 (73.6, 96.5)	72.8 (65.9, 99.6)	86.8 (76.2, 96.5)	0.08
MDRD	81.9 (72.8, 93.5)	71.4 (65.9, 96)	83.4 (74.4, 93.4)	0.09
HIV laboratory parameters				
CD4 count, cells/ μ l	489 (341, 638)	470 (394.3, 545.8)	502 (333, 660)	0.55
CD4 percent	29 (22, 36)	24 (18.3, 34.8)	30 (22, 37)	0.10
Nadir CD4 count, cells/ μ l	150 (38, 267)	92 (35.3, 193.8)	180 (41.3, 275)	0.20
HIV RNA <50 copies/ml, n (%)	94 (85)	17 (85)	77 (84.6)	1.00
Currently receiving ART				
Tenofovir, n (%)	83 (74.8)	17 (85)	66 (72.5)	0.39
Ritonavir, n (%)	43 (38.7)	8 (40)	35 (38.5)	0.90
Currently receiving ACE inhibitor/ARB, n (%)	29 (26)	12 (60)	17 (19)	<0.001
Hepatitis C infection, n (%)	12 (10.8)	2 (10)	10 (11)	1.00

Continuous variables listed as median (Q1, Q3).

GFR, glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; ART, antiretroviral therapy; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

copies/ml. The median current CD4 count was 489 cells/ μ l. Eighteen subjects (16%) had moderately increased albuminuria, and two subjects (1.8%) had severely increased albuminuria. The median GFR values measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and by the Modification of Diet in Renal Disease (MDRD) Study equation^{23,24} were 85.4 and 81.9 ml/min, respectively, with a median creatinine of 1.0 mg/dl. Almost 75% of patients were given tenofovir.

Demographic, clinical, and laboratory data compared between patients with and without albuminuria are also shown in Table 1. Patients with albuminuria were older and there was a higher proportion of hypertensive patients in this group. The Framingham risk score was significantly higher in patients with albuminuria. A higher proportion of patients with albuminuria fell in the Framingham high risk category (55% vs. 12%). Creatinine and GFR measured by CKD-EPI and MDRD were similar in both groups. The percentage of patients with undetectable HIV RNA, taking tenofovir or ritonavir, and CD4 counts were not significantly different between groups. The rate of hepatitis C infection was also similar between groups. The percentage of patients with current use of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) was higher in patients with albuminuria.

Inflammatory biomarker values were log-transformed as the data were more normally distributed posttransformation, except for sVCAM-1. Simple logistic regression analysis was performed to screen for associations between soluble inflammatory biomarkers and albuminuria. sE-selectin, sVCAM-1, tPAI-1, CRP, SAA, SAP, IL-1 β , IL-8, and TNF- α were associated with the presence of albuminuria at a *p*-value of 0.1 or less (Table 2). The aforementioned biomarkers were further analyzed by a multivariable logistic regression model adjusted for Framingham risk category (Table 2). Only sE-selectin, sVCAM-1, CRP, SAA, and SAP remained significantly associated with albuminuria.

Discussion

Albuminuria is more prevalent in HIV-infected individuals, and it has been shown to be associated with a higher rate of subclinical atherosclerosis and CVD.^{3,10,25} The pathophysiological mechanism linking albuminuria to CVD is unresolved. However, it has been proposed that it may be due to low-grade inflammation of the vessel wall characterized by endothelial dysfunction and transendothelial migration of leukocytes.²⁶ A myriad of previous studies in HIV-seronegative adults have shown the association between inflammatory biomarkers and albuminuria. Hence, we hypothesized

TABLE 2. MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS OF SOLUBLE BIOMARKERS AS PREDICTORS OF ALBUMINURIA

Soluble biomarker	Simple logistic regression				Multivariable logistic regression			
	Odds ratio	p-value	95% conf. interval		aOR ^a	p-value	95% conf. interval	
CRP	2.80	0.01*	1.28	6.12	3.01	0.02*	1.19	7.6
SAA	2.65	0.009*	1.28	5.47	2.45	0.02*	1.15	5.22
SAP	81.8	0.001*	5.74	1166	67.3	0.004*	3.85	1,181
sE-Selectin	28.6	0.01*	2.24	365	38.4	0.01*	2.25	653
sVCAM-1	1.003	0.006*	1.001	1.004	1.003	0.02*	1.001	1.005
sICAM-1	3.48	0.35	0.26	46.8	3.15	0.43	0.19	53.4
IL-1 β	54.7	0.09	0.55	5422	36.6	0.10	0.50	2,678
IL-6	2.48	0.21	0.60	10.2	1.74	0.48	0.37	8.25
IL-8	33.0	0.04*	1.22	890	21.9	0.10	0.57	837
IL-10	0.73	0.40	0.36	1.50	0.63	0.27	0.28	1.44
TNF- α	10.7	0.04*	1.09	105	10.2	0.06	0.93	112
IFN- γ	0.71	0.61	0.19	2.61	0.9	0.88	0.22	3.59
MCP-1	4.36	0.44	0.10	184	2.61	0.61	0.06	110
MMP-9	1.47	0.71	0.20	11.1	2.09	0.48	0.26	16.6
MPO	2.39	0.41	0.30	19.3	2.01	0.55	0.18	23.7
tPAI-1	8.94	0.08	0.77	104	7.16	0.15	0.50	103
VEGF	0.87	0.86	0.18	4.12	0.48	0.40	0.09	2.6

^aaOR, adjusted odds ratio; separate multivariable logistic regression models were conducted for each soluble biomarker adjusting for Framingham risk category.

*Statistically significant.

Values were log-transformed prior to analysis, except for sVCAM-1.

IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; MPO, myeloperoxidase; t PAI-1, tissue plasminogen activator inhibitor-1; VEGF, vascular endothelial growth factor.

that chronic inflammation is likely associated with albuminuria in HIV-seropositive individuals as well. In addition, we postulated that this relationship would persist despite being on antiretroviral medications, particularly in virologically suppressed HIV-infected individuals, as a previous study has shown persistent elevation of cytokines and cell adhesion molecules in HIV-seropositive patients who had been on combination antiretroviral therapy for 12 years.²⁷

In this study we found the associations of albuminuria and soluble cell adhesion molecules including sE-selectin and sVCAM-1 as well as acute phase reactants (CRP, SAA, SAP). The majority of our patient population has well-controlled HIV disease with a mean CD4 count of 489 and 85% with undetectable HIV RNA. This supports the notion that there is ongoing chronic inflammation in HIV patients who receive combination antiretroviral therapy.

The correlation between albuminuria and sVCAM-1, sE-selectin, CRP, SAA, and SAP we found in this study was proved to be independent of traditional risk factors including diabetes mellitus, hypertension, CVD, total cholesterol, HDL cholesterol, smoking, age, and gender that were included in the composite FRS. We did not find an association between albuminuria and CD4 count, number of patients with undetectable HIV RNA, and antiretroviral therapy use including tenofovir, which potentially cause renal tubular toxicity,¹¹ and ritonavir, which was associated with albuminuria in a previous study.¹ A previous study also showed that hepatitis C was associated with albuminuria.⁴ However, we did not find a significant difference in hepatitis C prevalence among patients with and without albuminuria. Obesity and low adiponectin level were reported to be associated with albuminuria.²⁸ However, body mass index (BMI) was similar in both groups. As a result we did not include these factors in the multivariable logistic regression model. This study suggests

that HIV-induced chronic inflammation contributes to endothelial dysfunction. Additionally, patients with albuminuria had a higher percentage of ACE inhibitor and/or ARB use. Without using these medications, albuminuria might have been higher in this group.

VCAM-1 and E-selectin (or endothelial-leukocyte adhesion molecule 1, ELAM-1) are inducible endothelial cell adhesion molecules that play a role in the recruitment of leukocytes into sites of inflammation. VCAM-1 has been shown in numerous studies to be associated with albuminuria in the general population and in individuals with type 1 and type 2 diabetes mellitus with or without hypertension and IgA nephropathy.^{26,29–34} In addition, elevated circulating VCAM-1 has been shown to be correlated with increased VCAM-1 expression from renal biopsy in IgA nephropathy.³⁵ E-selectin is also found to be a strong predictor of severely increased albuminuria and coronary artery disease in patients with type 1 diabetes.^{36,37} In another study VCAM-1 and E-selectin showed positive associations with retinopathy, albuminuria, and CVD.³⁸ In the HIV population, VCAM-1 was significantly elevated in both HIV-infected adolescents who received antiretroviral therapy and who were treatment naive.³⁹ Other studies showed higher VCAM-1 and E-selectin levels in adult HIV patients with and without treatment,^{40,41} and they were a potential marker of disease progression and death.^{42,43} Recently, VCAM-1 was found to be associated with greater carotid intima media thickness in another study from our group.⁴⁴ Our current study is the first study showing the association of VCAM-1 and E-selectin with albuminuria in HIV-infected patients.

SAA levels have been reported to increase in response to inflammation and infection similar to CRP, and to be expressed in cells of human atherosclerotic lesions, including endothelial cells, and in human cultured smooth muscle cells and monocyte-macrophage cell lines.^{45–47} SAA is implicated

in cholesterol metabolism and transport as SAA can displace apoA-1 from HDL. Thus, it might influence HDL clearance of excess cellular cholesterol.⁴⁵ Acute phase reactants, CRP and SAA, have been reported to be associated with albuminuria in the general population and patients with type 2 diabetes.^{14,25,48–50}

SAP, a biomarker in the same pentraxin family as CRP, functions in innate immunity and inflammation. Its expression is regulated by proinflammatory cytokines including TNF- α , IL-1 β , and IL-6. SAP is a vital component of extracellular matrices, particularly glomerular basement membranes. SAP has been identified in atherosclerotic lesions, and was found to be associated with angina and myocardial infarction.⁵¹ One study using immunofluorescence and anti-SAP antibody produced abnormal staining patterns in renal biopsy specimens from patients with diabetes and other renal diseases.⁵² Hence, SAP may play roles in both atherosclerosis and renal diseases.

VCAM-1 and E-selectin, markers of endothelial dysfunction, were strongly and independently associated with proinflammatory cytokines. Acute phase reactant expression is regulated by proinflammatory cytokines.^{45,51,53,54} In simple logistic regression analysis, we found the association of TNF- α , and IL-8 with albuminuria, but these were not significant after adjustment for Framingham risk category.

There are several limitations in our study. First, the nature of our study is cross-sectional and lacked an HIV-seronegative control group. Although not all subjects in the cohort had urine albumin collected at their visit, there was no systematic selection or exclusion of these subjects on review.

Second, our study obtained only a single random urine sample for albumin measurement. A 24-h urine sample may yield greater precision in measuring albumin excretion, although a spot urine sample has been proposed as an accurate estimate of albumin excretion.^{55–58} Due to an intraindividual day-to-day variation of urinary albumin excretion, it is often suggested that elevated urinary albumin excretion should be confirmed in at least two samples. Nonetheless, a recent population-based prospective long-term follow-up study has shown that one specimen was sufficient to show a significant association with cardiovascular mortality if the threshold for albuminuria is above 1.7 mg/mmol.⁵⁹ If a lower threshold is used, then more than one specimen would be better for cardiovascular death prediction. The threshold we used in our study was ≥ 3 mg/mmol (≥ 30 mg/g), well above this cut off, suggesting that the one sample was adequate.

Third, our study was limited by a small sample size and therefore could not adjust for all baseline characteristics such as age, hypertension, and the use of ACE inhibitors and/or ARBs, as well as HIV-related factors. However, we did adjust for FRS, which is a better surrogate of CAD that includes age, systolic blood pressure, and treatment for hypertension. The significant findings on multivariable regression adjusted for Framingham risk category accounted for the multiple comparisons for each biomarker. Due to the small sample size, our multivariable logistic regression analyses did not include all biomarkers that were significant in the simple logistic regression analyses in a single model. A larger study that can account for these multiple comparisons of targeted biomarkers should be performed to validate these findings. HIV-related factors including HIV-RNA, CD4 count, and CD4 percent did not differ significantly in the simple logistic regression analysis. Analysis into toxicity to classes of anti-

retroviral therapy was limited, but no obvious correlations were noted with specific tenofovir use. Finally, this study suggests the associations between inflammatory biomarkers with albuminuria, but it would be premature to conclude a causal relationship between these factors. Further study is needed to clarify this relationship.

Conclusions

Our study found that the presence of albuminuria in HIV-infected adults on cART is associated with increased levels of soluble cell adhesion molecules VCAM-1 and E-selectin and increased levels of acute phase reactants CRP, SAA, and SAP. These inflammatory biomarkers merit further study in terms of pathophysiological mechanism and potential biomarkers for albuminuria among HIV-infected individuals who are on cART.

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