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Original Investigation

Serum Albumin and Kidney Function Decline in HIV-Infected Women

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Background: Serum albumin concentrations are a strong predictor of mortality and cardiovascular disease in human immunodeficiency virus (HIV)-infected individuals. We studied the longitudinal associations between serum albumin levels and kidney function decline in a population of HIV-infected women.

Study Design: Retrospective cohort analysis.

Setting & Participants: Study participants were recruited from the Women's Interagency HIV Study (WIHS), a large observational study designed to understand risk factors for the progression of HIV infection in women living in urban communities. 908 participants had baseline assessment of kidney function and 2 follow-up measurements over an average of 8 years.

Predictor: The primary predictor was serum albumin concentration.

Outcomes: We examined annual change in kidney function. Secondary outcomes included rapid kidney function decline and incident reduced estimated glomerular filtration rate (eGFR).

Measurements: Kidney function decline was determined by cystatin C–based ($eGFR_{cys}$) and creatinine-based eGFR ($eGFR_{cr}$) at baseline and follow-up. Each model was adjusted for kidney disease and HIV-related risk factors using linear and relative risk regression.

Results: After multivariate adjustment, each 0.5-g/dL decrement in baseline serum albumin concentration was associated with a 0.56-mL/min faster annual decline in $eGFR_{cys}$ ($P < 0.001$), which was attenuated only slightly to 0.55 mL/min/1.73 m^2 after adjustment for albuminuria. Results were similar whether using $eGFR_{cys}$ or $eGFR_{cr}$. In adjusted analyses, each 0.5-g/dL lower baseline serum albumin level was associated with a 1.71-fold greater risk of rapid kidney function decline ($P < 0.001$) and a 1.72-fold greater risk of incident reduced eGFR ($P < 0.001$).

Limitations: The cohort is composed of only female participants from urban communities within the United States.

Conclusions: Lower serum albumin levels were associated strongly with kidney function decline and incident reduced eGFRs in HIV-infected women independent of HIV disease status, body mass index, and albuminuria.

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INDEX WORDS: Albumin; kidney function; HIV (human immunodeficiency virus); incident reduced estimated glomerular filtration rate (eGFR); albuminuria; disease trajectory; chronic kidney disease (CKD) progression.

Advances over the past 20 years in the treatment of human immunodeficiency virus (HIV) infection have led to increased life expectancy, yet adjusted mortality rates remain significantly elevated compared with noninfected individuals.[1] Chronic kidney disease (CKD) is one of the most important morbidities in this population, accounting for 17% of mortality risk.[2-4]

Risk factors for the onset of CKD and progression to end-stage renal disease (ESRD) in the setting of HIV infection appear to be both infection related

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(CD4 lymphocyte count, HIV viral load, and hepatitis C virus [HCV] coinfection) and non–infection related (hypertension, diabetes, and cardiovascular disease).[4] Serum albumin is a widely available routine clinical test and serves as a marker of acute and chronic disease.[5-7] Decreased serum albumin level has been associated strongly with mortality and cardiovascular disease in HIV-infected populations.[8-10] A previous study in an elderly population demonstrated that decreased albumin concentrations were associated more strongly with declining kidney function than several inflammatory markers, including C-reactive protein, interleukin 6, and D-dimer.[11] However, to our knowledge, no study has examined the associations of serum albumin concentrations with kidney function decline in the setting of HIV infection.

We hypothesized that lower serum albumin concentrations would be associated with faster decline in kidney function in HIV-infected individuals independent of markers of HIV viral load, albuminuria, and inflammation. To investigate this hypothesis, we conducted a longitudinal study nested within a nationally representative cohort of ethnically diverse HIV-infected women.

METHODS

Study Population

We included 908 HIV-infected women participating in the Women's Interagency HIV Study (WIHS), a large observational study designed to understand risk factors for the progression of HIV infection in women. Three participants were missing serum albumin measures and therefore only 905 are included in Table 1; those 3 without serum albumin were included in the regression analysis for multiple imputation of any missing covariates. The WIHS design and methods have been described previously.[12] Women were recruited from 6 US urban communities (Bronx, NY; Brooklyn, NY; Chicago, IL; Los Angeles, CA; San Francisco, CA; and Washington, DC) to be representative of the HIV-infected population. Participants are interviewed and examined every 6 months. Serum specimens are stored at −80°C until biomarker measurement.

The WIHS HIV Kidney Aging Study was designed to investigate the onset of kidney disease in the setting of HIV using stored urine and serum specimens. The baseline visit for this ancillary study was conducted from October 1999 through March 2000. Follow-up lasted an average of 8 (interquartile range, 7.5-8.1) years. One thousand HIV-infected and 250 uninfected women were included. Of these women, 450 were sampled from the WIHS bone substudy and 800 were selected at random, including age- and race-matched uninfected controls. There were no exclusions based on race or ethnicity. For this study, 908 HIV-infected women who had stored urine available and at least one follow-up visit were included. The WIHS was approved by the institutional review boards at all study sites. The WIHS HIV Kidney Aging Study also was approved by the University of California, San Francisco; San Francisco Veterans Affairs Medical Center; and Yale committees on human research.

Predictors

The primary predictor in this study was serum albumin concentration. Albumin measurements were conducted at each clinical site using albumin assays from Clinical Laboratory Improvement Amendments–certified laboratories. We evaluated serum albumin level as a continuous variable and dichotomized at 3.8 g/dL. The cutoff of 3.8 g/dL was chosen because it represented the lowest quartile of serum albumin concentrations in the study population. Serum albumin was measured at 6-month intervals as part of the WIHS core examination. We evaluated baseline serum albumin concentration, as well as changes in albumin levels, calculated from the baseline visit of the study to the last follow-up visit. Additional analyses included measurements of average albumin concentration over the entire study.

Secondary predictors included baseline cystatin C–based estimated glomerular filtration rate ($eGFR_{cys}$), urine albumin-creatinine ratio (ACR), CD4 count, and HIV RNA. Baseline $eGFR_{cys}$ was calculated as a continuous and dichotomous (<60 or ≥ 60 mL/min/1.73 m^2) predictor. Similarly, ACR was modeled as a continuous and dichotomous (<30 or ≥ 30 mg/g) predictor. HIV RNA value was log-transformed for analysis and also was dichotomized ($<1{,}000$ or $\geq 1{,}000$ copies/mL; $<10{,}000$ or $\geq 10{,}000$ copies/mL). CD4 cell count also was log-transformed and discretized (<200, 200-350, 351-500, and >500 cells/μL).

Outcomes

eGFR was determined using the 2012 CKD-EPI (CKD Epidemiology Collaboration) cystatin C equation ($eGFR_{cys}$). Cystatin C was measured at the baseline visit and years 4 and 8 of follow-up. Cystatin C was chosen because it is less biased by muscle mass and health status than creatinine and thus may be more reliable in the setting of HIV infection. It also has been shown to predict mortality better than creatinine level in the setting of HIV.[2,13] Additional analyses evaluated GFR using the CKD-EPI creatinine equation ($eGFR_{cr}$) and a combined creatinine–cystatin C equation.[14] We analyzed eGFR as a continuous outcome, expressed as annual change in eGFR in milliliters per minute per 1.73 m^2 over the 8 years of follow-up. Secondary outcomes included the following: rapid kidney function decline, defined as a decrease in kidney function $> 5\%$ per year, using baseline and final $eGFR_{cys}$; and incident reduced eGFR, defined as final eGFR < 60 mL/min/1.73 m^2.

Covariates

Candidate covariates included demographic characteristics, traditional risk factors for kidney disease, markers of inflammation, and HIV-related risk factors. The following characteristics were tested as candidate covariates in all multivariate models: age, race/ethnicity, antihypertensive drug use, baseline eGFR, diabetes (defined by any of the following confirmed criteria: fasting glucose ≥ 126 mg/dL, self-reported diabetes, self-reported diabetes medication use, or hemoglobin $A_{1c} \geq 6.5\%$), cigarette smoking status (current, former, or never), systolic and diastolic blood pressures, low- and high-density lipoprotein cholesterol levels, triglyceride level, body mass index, urine ACR (albuminuria), waist circumference, HCV infection (confirmed by detectable HCV RNA following a positive HCV antibody result), and current heroin use. The HIV-related risk factors included CD4 lymphocyte count, history of AIDS diagnosis, HIV viral load, and antiretroviral therapy. We modeled antiretroviral therapy use based on end-of-study treatment status (never, past, current, or new user of antiretroviral therapy). The antiretroviral therapies included current combination antiretroviral therapy use, current nucleoside reverse-transcriptase inhibitor use, current non-nucleoside reverse-transcriptase inhibitor use, and current protease inhibitor use. Additionally, all models were adjusted for study site in order to account for the possibility of differences in laboratory assays at each location.

Statistical Analyses

We compared clinical characteristics of dichotomized baseline serum albumin concentrations using Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables. We evaluated unadjusted and adjusted associations of serum albumin level with the continuous outcome of annual mean $eGFR_{cys}$ change by using linear mixed models with random intercepts and slopes to account for repeated measurements for each participant. We used Huber-White standard errors, which are designed to be robust to non–normally distributed residuals. We estimated the incidence rate ratio for binary outcomes (rapid kidney function decline and incident reduced eGFR) using relative risk regression. A Poisson working model was employed, using a robust variance estimator, which has fewer convergence problems than the log binomial model and gives an unbiased estimate of relative risk when the response variable is binary rather than Poisson.[15] We performed additional analyses testing interactions of albumin levels with ACR and viral load. Last, figures were created to examine whether these relationships were additive or multiplicative. Interaction tests and figures were included to verify that the association of serum albumin level with kidney function decline was not conditional on the presence or absence of albuminuria or the patient's level of HIV viral load control.

We initially used stepwise backward selection with a significance level of $\alpha = 0.05$ to remove candidate covariates that were not associated with linear kidney function decline. Factors forced into the full model included age, race/ethnicity, systolic and diastolic blood pressures, body mass index, antiretroviral therapy use, HCV infection, and study site. The final model for each outcome included age, race/ethnicity, systolic and diastolic blood pressures, body mass index, baseline eGFR, log HIV RNA, CD4 count, antiretroviral therapy use, and study site.

All analyses were conducted using the SAS system, version 9.2 (SAS Institute Inc).

RESULTS

At baseline, median age was 41 years and 58% of participants were African American. Median follow-up was 7.9 (interquartile range, 7.5-8.1) years, and median $eGFR_{cys}$ was 89 mL/min/1.73 m^2. Individuals with lower serum albumin concentrations (<3.8 g/dL) were more likely to be African American, current smokers, and hypertensive and have lower $eGFR_{cys}$ values, as well as lower low- and high-density lipoprotein cholesterol levels compared with participants with higher serum albumin levels (Table 1). Comparisons between WIHS participants who are included and excluded from this study are shown in Table S1 (provided as online supplementary material). Lower serum albumin concentrations also were associated with worse HIV disease status (as indicated by lower CD4 counts and higher HIV viral loads), less antiretroviral use, and higher prevalence of HCV coinfection. Rates of incident reduced eGFR and rapid kidney function decline were higher for those with low serum albumin concentrations (<3.8 g/dL) than for those with normal levels. Similarly, the annual change for these 2 groups differed by ~0.6 mL/min. The overall annual change in eGFR for the entire cohort was −1.54 mL/min/1.73 m^2 per year (95% confidence interval [CI], −1.74 to −1.34).

As a linear variable, serum albumin concentrations were associated strongly with declining kidney function (Table 2). The finding was attenuated minimally by albuminuria. Baseline urine ACR also was associated with declining kidney function. Furthermore, there was no significant interaction of serum albumin concentration with HIV RNA level or ACR ($P = 0.2$ and $P = 0.08$, respectively).

Dichotomized serum albumin concentrations (<3.8 vs ≥3.8 g/dL) produced similar results as linear declines (Table 2). Results also remained equivalent using both the creatinine-based CKD-EPI equation (Table S2) and a combined creatinine–cystatin C eGFR equation to define the outcomes. Dichotomized ACR (<30 vs ≥30 mg/g) also predicted declining kidney function after adjustment for serum albumin concentration (Table 2).

Lower serum albumin levels were associated with both rapid kidney function decline and incident reduced eGFR (Table 3). Continuous declines in ACR were associated weakly with both rapid kidney function decline and incident reduced eGFR; however, dichotomized ACR values were the strongest predictor of both rapid kidney function decline and incident reduced eGFR.

Baseline HIV viremia also was associated independently with rapid kidney function decline (Table 4). After multivariable adjustment excluding serum albumin level, each 10-fold higher baseline HIV RNA level was associated with a 56% increased risk of rapid kidney function decline. However, when serum albumin level was included as a covariate in the same model, the effect size of HIV RNA was attenuated to 39%. In analyses of change in HIV RNA level and average HIV RNA level, serum albumin level attenuated the point estimates by a similar proportion. We also evaluated associations of CD4 count with kidney function decline and found a nonsignificant association in adjusted analyses (−0.026 [95% CI, −0.20 to 0.15] mL/min/1.73 m^2 per year per doubling of CD4 count).

Joint associations of baseline HIV RNA (<1,000 vs ≥1,000 copies/mL) and serum albumin levels (<3.8 vs ≥3.8 g/dL) with rapid decline also were examined (Fig 1). The prevalence of rapid decline was highest in those who had both low albumin and high HIV RNA levels (26%), intermediate in those with low albumin levels alone or high HIV RNA levels (20% and 13%, respectively), and lowest in those with neither low albumin level nor high HIV RNA level (8%). We performed a similar analysis for serum albumin concentrations (<3.8 g/dL) and ACR (>30 mg/g; Fig 2), which demonstrated additive risk for rapid kidney function decline.

Table 1. Baseline Characteristics of HIV-Infected WIHS Participants, Stratified by Serum Albumin

	<3.8 g/dL (n = 214)	≥3.8 g/dL (n = 691)	*P*
Parameter			
Baseline age	42 [37-47]	41 [36-45]	0.02
<30 y	12 (6)	43 (6)	
30-39.9 y	68 (32)	280 (41)	
40-49.9 y	114 (53)	295 (43)	
≥50 y	20 (9)	73 (11)	
Race			<0.001
African American	143 (67)	379 (55)	
White	21 (10)	153 (22)	
Other	50 (23)	159 (23)	
Menopause	55 (26)	130 (19)	0.03
Cigarette smoking			0.001
Current	132 (62)	331 (48)	
Past	37 (17)	186 (27)	
Never	45 (21)	174 (25)	
Diabetes mellitus	20 (9)	66 (10)	0.9
Systolic BP (mm Hg)	120 [108-130]	118 [108-128]	0.08
Diastolic BP (mm Hg)	72 [66-80]	71 [65-80]	0.2
Hypertension	76 (36)	151 (22)	<0.001
Antihypertensive use	32 (15)	66 (10)	0.03
LDL cholesterol (mg/dL)	95 [74-119]	107 [82-135]	<0.001
HDL cholesterol (mg/dL)	41 [32-50]	45 [36-57]	<0.001
Triglycerides (mg/dL)	131 [95-182]	134 [92-201]	0.6
BMI (kg/m^2)	27 [23-32]	26 [23-31]	0.5
Waist circumference (cm)	88 [79-101]	88 [80-99]	0.8
Current cART use	112 (52)	419 (61)	0.03
Current NRTI use	123 (57)	480 (69)	0.002
Current NNRTI use	50 (23)	194 (28)	0.2
Current PI use	80 (37)	299 (43)	0.1
Current CD4 count (cells/μL)	337 [197-517]	414 [254-587]	0.001
Nadir CD4 count (cells/μL)	200 [100-330]	214 [113-324]	0.4
History of AIDS (CD4 or OI)	122 (57)	322 (47)	0.008
Plasma HIV RNA category			0.005
≤80 copies/mL	48 (23)	226 (33)	
81-1,999 copies/mL	45 (21)	159 (23)	
2,000-9,999 copies/mL	37 (17)	109 (16)	
≥10,000 copies/mL	83 (39)	192 (28)	
Hepatitis C virus infection	89 (42)	192 (28)	<0.001
Current heroin use	13 (6)	30 (4)	0.4
$eGFR_{cys}$ (mL/min/1.73 m^2)	81 [68-96]	92 [77-106]	<0.001
$eGFR_{cr}$ (mL/min/1.73 m^2)	104 [82-120]	96 [81-112]	0.01
Urine ACR (mg/g)	11.7 [6.0-32.3]	9.7 [6.0-20.9]	0.1
Outcome			
Incident reduced eGFR[a]	46/174 (26)	101/646 (16)	0.002
Rapid kidney function decline[b]	50/214 (23)	73/691 (11)	<0.001
Annual change in eGFR (mL/min/1.73 m^2)	−2.01 [−2.50 to −1.51]	−1.41 [−1.63 to −1.20]	0.005

Note: Values for categorical variables are given as number or n/N (percentage); values for continuous variables, as median [interquartile range].

Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; BP, blood pressure; cART, combination antiretroviral therapy; eGFR, estimated glomerular filtration rate; $eGFR_{cr}$, creatinine-based estimated glomerular filtration rate; $eGFR_{cys}$, cystatin C–based estimated glomerular filtration rate; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; OI, opportunistic infection; PI, protease inhibitor; WIHS, Women's Interagency HIV Study.

[a]Incident reduced eGFR defined as eGFR < 60 mL/min/1.73 m^2.

[b]Defined as >5% per year, using baseline and final $eGFR_{cys}$.

DISCUSSION

We found that serum albumin concentration was a strong and independent risk factor for kidney function decline in this cohort of HIV-infected women. These findings remained robust in analyses of serum albumin level as a linear or dichotomous outcome and using outcomes based on $eGFR_{cys}$, $eGFR_{cr}$, or combined creatinine–cystatin C eGFR. For the clinical end

Table 2. Associations of Serum Albumin Concentration With Annual Change in $eGFR_{cys}$ in HIV-Infected WIHS Participants

	Unadjusted Estimate (95% CI)	*P*	Adjusted Without ACR[a] Estimate (95% CI)	*P*	Adjusted With ACR[a] Estimate (95% CI)	*P*
Continuous predictors						
Serum albumin, per 0.5-g/dL less	−0.44 (−0.59 to −0.28)	<0.001	−0.56 (−0.72 to −0.39)	<0.001	−0.55 (−0.71 to −0.39)	<0.001
ACR, per doubling	−0.22 (−0.31 to −0.14)	<0.001			−0.28 (−0.36 to −0.20)	<0.001
Baseline $eGFR_{cys}$, per 10–mL/min/1.73 m^2 greater	−0.28 (−0.37 to −0.20)	<0.001	−0.47 (−0.56 to −0.39)	<0.001	−0.53 (−0.62 to −0.45)	<0.0001
Dichotomized predictors						
Serum albumin < 3.8 g/dL	−0.43 (−0.74 to −0.13)	0.005	−0.43 (−0.75 to −0.12)	0.007	−0.42 (−0.73 to −0.10)	0.009
ACR ≥ 30 mg/g	−0.50 (−0.96 to −0.047)	0.03			−0.61 (−1.08 to −0.15)	0.009
Baseline $eGFR_{cys}$ < 60 mL/min/1.73 m^2	1.15 (0.54 to 1.76)	<0.001	1.53 (0.91 to 2.1)	<0.001	1.73 (1.09 to 2.4)	<0.001

Note: Results reported as estimated annual change (95% CI) in $eGFR_{cys}$ calculated from multivariable linear mixed models.

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; $eGFR_{cys}$, cystatin C–based estimated glomerular filtration rate; HIV, human immunodeficiency virus; WIHS, Women's Interagency HIV Study.

[a]Adjusted models control for age, race, HIV RNA level, CD4 count, hepatitis C virus, diabetes mellitus, antiretroviral therapy use, baseline eGFR, systolic and diastolic blood pressures, body mass index, and study site. For ACR as a predictor, instead of adjusting for ACR, the full model adjusts for serum albumin concentration. Antiretroviral therapy included current combination antiretroviral therapy use, current nucleoside reverse-transcriptase inhibitor use, current non-nucleoside reverse-transcriptase inhibitor use, and current protease inhibitor use.

points of rapid kidney function decline and incident reduced eGFR, each 0.5-g/dL lower baseline serum albumin concentration was associated with an ~60% increased risk. Furthermore, not only was serum albumin level a stronger risk factor than viral load, it also appeared to attenuate the association of HIV viral load with rapid kidney function decline. Serum albumin concentration < 3.8 g/dL had similar strength of association with kidney function decline as urine ACR ≥ 30 mg/g.

Numerous studies have examined the associations of serum albumin levels with adverse events in HIV-infected individuals.[8-10,16,17] However, no previous studies, to our knowledge, have evaluated the

Table 3. Multivariable-Adjusted Associations of Serum Albumin With Rapid Kidney Function Decline and Incident Reduced eGFR in HIV-Infected WIHS Participants

	Rapid Kidney Function Decline		Incident Reduced $eGFR_{cys}$	
	Adjusted IRR (95% CI)	*P*	Adjusted IRR (95% CI)	*P*
Continuous predictors				
Serum albumin, per −0.5-g/dL less	1.71 (1.29-2.26)	<0.001	1.72 (1.31-2.25)	<0.001
ACR, per doubling	1.19 (1.09-1.31)	<0.001	1.13 (1.00-1.27)	0.04
Baseline $eGFR_{cys}$, per 10–mL/min/1.73 m^2 greater	0.98 (0.90-1.07)	0.7	1.41 (1.22-1.64)	<0.001
Dichotomized predictors				
Serum albumin < 3.8 g/dL	2.13 (1.30-3.49)	0.003	1.71 (1.05-2.79)	0.03
ACR ≥ 30 mg/g	2.03 (1.28-3.20)	0.002	1.95 (1.19-3.20)	0.008
Baseline $eGFR_{cys}$ < 60 mL/min/1.73 m^2	1.05 (0.62-1.77)	0.9	NA[a]	

Note: Rapid kidney function decline defined as >5% per year, using baseline and final $eGFR_{cys}$. Results reported as relative risk of rapid kidney function decline or incident reduced $eGFR_{cys}$ (95% CI). Estimates are calculated from generalized estimating equation relative risk regression models. Models control for age, race, HIV RNA level, CD4 count, hepatitis C virus, diabetes mellitus, antiretroviral therapy use, baseline eGFR, systolic and diastolic blood pressures, body mass index, ACR, and study site. For ACR as a predictor, instead of adjusting for ACR, the full model adjusts for serum albumin concentration. Antiretroviral therapy included current combination antiretroviral therapy use, current nucleoside reverse-transcriptase inhibitor use, current non-nucleoside reverse-transcriptase inhibitor use, and current protease inhibitor use.

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; $eGFR_{cys}$, cystatin C–based estimated glomerular filtration rate; HIV, human immunodeficiency virus; IRR, incidence rate ratio; NA, not applicable; WIHS, Women's Interagency HIV Study.

[a]Analysis of incident reduced eGFR excludes those with reduced eGFR at baseline. Model instead controls for continuous eGFR.

Table 4. Multivariable-Adjusted Associations of HIV Viral Load With Rapid Kidney Function Decline by $eGFR_{cys}$ in HIV-Infected WIHS Participants

	Unadjusted IRR (95% CI)	*P*	Adjusted Without Serum Albumin[a] IRR (95% CI)	*P*	Adjusted With Serum Albumin[a] IRR (95% CI)	*P*
Baseline HIV RNA, per 10-fold greater	1.38 (1.06-1.79)	0.02	1.56 (1.19-2.06)	0.001	1.39 (1.11-1.73)	0.003
Mean HIV RNA, per 10-fold greater	1.44 (1.02-2.01)	0.04	1.46 (1.10-1.94)	0.009	1.31 (1.02-1.67)	0.03

Note: Rapid kidney function decline defined as >5% per year, using baseline and final $eGFR_{cys}$. Results reported as relative risk of rapid kidney function decline (95% CI). Estimates are calculated from generalized estimating equation relative risk regression models.

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; $eGFR_{cys}$, cystatin C–based estimated glomerular filtration rate; HIV, human immunodeficiency virus; IRR, incidence rate ratio; WIHS, Women's Interagency HIV Study.

[a]Models control for age, race, HIV RNA level, CD4 count, hepatitis C virus, diabetes mellitus, antiretroviral therapy use, baseline eGFR, systolic and diastolic blood pressures, body mass index, ACR, and study site. For ACR as a predictor, instead of adjusting for ACR, the full model adjusts for serum albumin concentration. Antiretroviral therapy included current combination antiretroviral therapy use, current nucleoside reverse-transcriptase inhibitor use, current non-nucleoside reverse-transcriptase inhibitor use, and current protease inhibitor use.

relationship between serum albumin level and longitudinal kidney function in an HIV-infected population, and few have studied serum albumin level and kidney disease in the general population.[11,18] In the Cardiovascular Health Study, each 0.4-g/dL lower baseline serum albumin level was associated with a 1.14 higher odds of rapid kidney function decline. Other studies have found serum albumin level to be an important risk factor for ESRD.[19,20]

Despite the surprisingly strong associations in this study, the underlying mechanisms are still unclear. To our knowledge, there is not a direct physiologic link between lower serum albumin concentration and kidney function decline. Serum albumin level may be depressed for one of several reasons, including extreme cases of poor nutrition, liver disease, albuminuria, and both acute and chronic inflammation. It is unlikely that decreased serum albumin concentrations reflect poor nutrition because the only condition of malnourishment showing consistently decreased serum albumin levels is kwashiorkor, a rare disease in the United States.[7] Significant albuminuria also can contribute to decreased albumin levels, but is unlikely to be a major cause in this population. Few participants in this study had high levels of albuminuria, with most having normal to moderately increased albuminuria. Furthermore, the median ACR was not much higher in those with low versus high serum albumin levels. Finally, the effects of serum albumin level and albuminuria are additive with regard to change in kidney function.

It is likely that several biological mechanisms contribute to serum albumin concentration reflecting a state of ill health. Liver disease may explain lower serum albumin levels, though our analyses adjust for rates of both hepatitis B virus and HCV infection. One other possible biological mechanism linking serum albumin concentration and kidney function is systemic inflammation. A number of studies have linked inflammatory markers to kidney disease.[18,21,22] Individuals infected with HIV, even those with a well-controlled viral load, are known

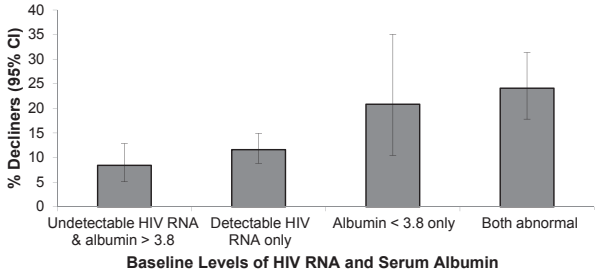

Figure 1. Association of serum albumin level and human immunodeficiency virus (HIV) RNA with rapid kidney function decline. Bars denote percentage of participants in each category with rapid kidney function decline (determined by cystatin C–based estimated glomerular filtration rate [$eGFR_{cys}$]), with 95% confidence intervals (CIs).

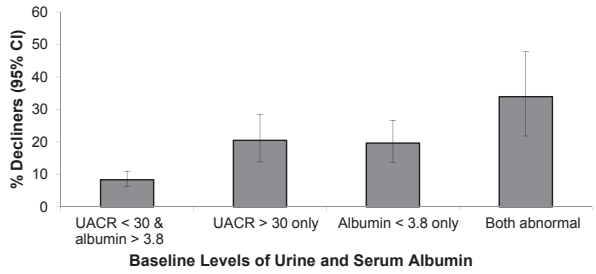

Figure 2. Association of serum albumin level and urine albumin-creatinine ratio (UACR) with rapid kidney function decline. Bars denote percentage of participants in each category with rapid kidney function decline (determined by cystatin C–based estimated glomerular filtration rate [$eGFR_{cys}$]), with 95% confidence intervals (CIs).

to have elevated concentrations of various inflammatory markers.[23,24] Moreover, in a study of 8 inflammatory markers and serum albumin and kidney function in an elderly population, serum albumin level was the only factor associated with kidney function decline.[18] In summary, serum albumin level likely reflects chronic illness through multiple mechanisms that remain unclear.

Our study had a large sample size, with rigorously ascertained clinical data collected over 8 years in a well-characterized cohort and repeated measurements of both cystatin C and creatinine. Our study also had several limitations. The WIHS is composed entirely of women and thus our findings may not be generalizable to men with HIV infection, women outside the United States, or the uninfected population. We also cannot fully explain the physiologic basis of the relationship between serum albumin concentration and kidney function decline.

In summary, we found that lower serum albumin levels were associated strongly with kidney function decline and incident reduced eGFR in HIV-infected women independent of HIV disease status and albuminuria. Lower concentration of serum albumin, a ubiquitously available laboratory test, may help clinicians plan future treatment or prevention efforts in the setting of HIV infection. Already studies in the general population and HIV-infected populations document serum albumin level as an important covariate in determining risk for ESRD.[4,25] including one widely used ESRD prediction tool.[26] Furthermore, laboratory experiments and future studies examining risk factors for serum albumin concentration declines may illuminate the biological link between HIV infection and kidney disease.

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Contributions: Research area and study design: JL, MGS; data acquisition: PCT, KA, AA, AS, MHC, AWB, MN, MME; data analysis/interpretation: JL, MGS, CG, CRP, RS, PCT, KA, AA, AS, MHC, AWB, MN, MME; statistical analysis: RS; supervision and mentorship: MGS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. MGS takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Baseline characteristics, stratified by inclusion/exclusion status.

Table S2: Associations of serum albumin concentration with annual change in $eGFR_{cr}$.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.05.015) is available at www.ajkd.org

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