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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.