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Cystatin C and Creatinine in An HIV Cohort: the Nutrition for Healthy Living Study

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Abstract

Background—Human immunodeficiency virus (HIV)-infected persons have increased risk of chronic kidney disease (CKD). Serum creatinine may underestimate prevalence of CKD in subjects with decreased lean body mass or liver disease. Serum cystatin C, an alternative kidney function marker, is independent of lean body mass.

Study Design—Cross-sectional

Setting and Participants—250 HIV-infected subjects taking highly active antiretroviral therapy in the Nutrition for Healthy Living (NFHL) cohort; 2628 NHANES 2001–2002 subjects.

Predictors and Outcomes—Comparison of serum creatinine in NFHL to NHANES subjects; comparison of CKD in NFHL subjects ascertained using serum creatinine versus cystatin C.

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Potential Conflicts of Interest:
Clara Y. Jones, MD: None
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Measurements—Standardized serum creatinine, serum cystatin C, glomerular filtration rate (GFR) estimated from serum creatinine and cystatin C.

Results—Creatinine was lower in NFHL than in NHANES despite higher rates of hepatitis, diabetes, and drug use (mean difference −0.18 mg/dl, p<0.001 adjusted for age, sex, and race). Among NFHL subjects, only 2.4% had creatinine-based estimated GFR <60ml/min/1.73m^2, but 15.2% had a cystatin-based estimated GFR <60 ml/min/1.73m^2.

Limitations—GFR was estimated rather than measured. Other factors beside GFR may affect creatinine and cystatin C levels. Measures of proteinuria were not available.

Conclusions—Serum creatinine may overestimate GFR in HIV-infected subjects. Kidney disease prevalence may be higher than previously appreciated.

Key phrases

HIV; Cystatin C; Creatinine; GFR; Kidney Disease; Hepatitis; Nutrition for Healthy Living

Introduction

People with human immunodeficiency virus (HIV) infection have an increased risk for kidney disease for a variety of reasons, including the high prevalence of hepatitis B and C co-infection [1–3], drug abuse [4], direct effects of HIV on kidney cells [5–9] and nephrotoxicity of several highly active antiretroviral (HAART) medications [10–14]. Kidney disease in HIV infected patients is associated with increased complications and utilization of health care resources [15–18]. Early detection of kidney disease in persons with HIV would allow for appropriate evaluation and treatment, as well as modification of medication regimens to avoid systemic toxicity and worsening of kidney function [19].

Chronic kidney disease (CKD) is defined as either kidney damage or reduced glomerular filtration rate (GFR) for three months or more [20]. Serum creatinine is the most commonly used index of GFR. However, the serum creatinine level is also determined by factors other than GFR, in particular creatinine generation due to muscle mass, the presence of liver disease, and diet [21;22]. Creatinine-based GFR estimating equations account for some of the variability in muscle mass based on age, sex, race and weight, however these equations overestimate GFR in patients who have lower creatinine generation for other reasons such as decreased hepatic synthesis of creatine, or abnormally decreased lean body mass. Because persons with HIV may have decreased lean body mass [23], and have a relatively high prevalence of liver disease, GFR estimates based on serum creatinine may be too high, and CKD may be overlooked. Serum cystatin C, a protein produced by all nucleated cells and cleared by glomerular filtration, is a promising alternative endogenous filtration marker which is not influenced by muscle mass [24] or liver function, and may therefore be a more accurate index of kidney disease in persons with HIV [25;25].

In this study we measured serum creatinine and serum cystatin C in 250 HIV-infected subjects taking HAART in the Nutrition for Healthy Living (NFHL) Study, and generated GFR estimates based on serum creatinine (eGFRcreat) and serum cystatin C (eGFRcys). Our objectives were to determine whether there were differences in creatinine levels in HIV-

infected subjects on HAART compared to persons of similar age, race and sex in the National Health and Nutrition Examination Survey 2001–2002 (NHANES) and to compare differences in prevalence of CKD when using creatinine-based versus cystatin C-based glomerular filtration rate (GFR) estimates in HIV infected subjects.

Methods

Participants

NFHL was a prospective cohort study of HIV and nutritional status in HIV infected adults (18 years of age or older) from Boston, Massachusetts and Providence, Rhode Island. Methods have been previously published [26]. In brief, questionnaires, laboratory studies, bioelectrical impedance analysis (BIA), and anthropometry measurements were obtained at baseline and at six-month intervals. Dual x-ray absorptiometry (DEXA) was obtained at two-year intervals. The protocol was approved by the Human Investigations Research Committees (HIRC) at the New England Medical Center in Boston, Massachusetts and at Miriam Hospital in Providence, Rhode Island and written informed consent was obtained from each participant. The NFHL study was funded in two cycles (September 1995 to August 2000, and September 2000 to August 2005). The second cycle added analysis of several metabolic parameters including insulin. The kidney function sub-study, which is the basis for this manuscript, was funded in November 2005 to analyze serum creatinine and serum cystatin on stored frozen serum samples for 250 HIV-infected subjects taking HAART. The goal of the sub-study was to study the association of kidney function parameters with metabolic complications of HIV infection, including insulin resistance. Therefore, of the 881 subjects ever enrolled in the NFHL study, only the 567 subjects who were in the study from September 2000 onward (for whom serum insulin was routinely obtained) were potentially eligible. The sub-study included subjects who were taking HAART for at least six months, had fasting insulin, glucose, alanine aminotransferase (ALT), high-density lipoprotein (HDL) and triglyceride results available, and had a dual x-ray absorptiometry scan either at the prior, same, or succeeding visit. All 76 women with eligible visits were included, and 174 men were randomly selected from the 216 men with eligible visits to achieve a total of 250 subjects. If a subject had more than one eligible visit, the earliest eligible visit was selected for this study. The demographics of the 250 subjects included in the sub-study are similar to both the total cohort (N=881), and to those active in the study after September 2000 (N=597) in age, sex, race, Body mass index (BMI), and history of injection drug use.

Data from 2628 NHANES 2001–2002 participants aged 20–50 years with available creatinine values were analyzed [27].

Variables

Measurement of Kidney Function—Serum creatinine for NFHL was determined on stored frozen samples in the Tufts-New England Medical Center (T-NEMC) clinical laboratory in January 2006 using the picric acid Jaffe rate method on the Beckman LX20 analyzer. Creatinine samples for NHANES 2001–2002 were analyzed at the White Sands Laboratory using the Jaffe kinetic alkaline picrate rate method.

Serum cystatin C for NFHL was measured on stored frozen samples at the Cleveland Clinic Laboratory using an automated particle-enhanced immunonephelometric assay (PENIA) on the N Latex Cystatin C, Dade Behring, IL.

Calibration of an analyte is important for optimal use of GFR estimating equations in populations other than those in which the equations were derived [28]. In 2006, the T-NEMC and NHANES 2001–2002 creatinine instruments were both calibrated to the Roche P-Module creatinine enzymatic assay at the Cleveland Clinic Research Laboratory, which has been shown to be equivalent to creatinine reference values [29–31](Selvin, E et al, Amer Jour Kid Disease, in press 2007). For T-NEMC, 200 samples were used. Linear regression was used to assess significance of the slope and intercept in comparison of the assigned creatinine values from the T-NEMC and Cleveland Clinic laboratories. Based on these calibration exercises, a value of 0.07 mg/dl (6 μmol/L) was subtracted from creatinine values reported from the Tufts-NEMC laboratory. No correction was required for the NHANES samples [27] (Selvin, E et al, Amer Jour Kid Disease, in press 2007). Thus all creatinine values reported in this study are standardized.

GFR Estimating Equations: GFR was estimated from creatinine using the isotope dilution mass spectrometry-traceable four-variable Modification of Diet in Renal Disease (MDRD) Study equation for standardized creatinine [29;32].

$$eGFRcreat=(175)\ (\text{serum creatinine})^{-1.154}\ (\text{age})^{-0.203}\ (0.742 \text{ if female})\ (1.21 \text{ if black})$$

GFR was estimated from cystatin C using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C GFR estimating equation [33]. Cystatin C for the CKD-EPI study was determined at the Cleveland Clinic Laboratory using an automated particle-enhanced immunonephelometric assay (PENIA) on the N Latex Cystatin C, Dade Behring, IL. This is the same laboratory and methods used for cystatin C in the NFHL sub-study. Thus there are no inter-laboratory calibration issues for cystatin C.

$$eGFRcys = 76.7*(\text{serum cystatin C}^{-1.18})$$

For both equations, eGFR is reported as ml/min/1.73m^2.

Other Variables

Age, race, and ethnicity were self-reported. BMI was calculated as weight (in kg) divided by height^2 (in meters). CD4 lymphocyte counts for NFHL participants were determined using a specific monoclonal antibody and fluorescence-activated cell-sorter analysis. HIV RNA viral load (VL) for NFHL participants was measured with the Roche Amplicor Monitor reverse transcriptase PCR assay (Roche Molecular Systems, Somerville, NJ, USA) (lower detection limit 400 copies/ml). If VL was undetectable, a value of 200 copies/ml was assigned for statistical analyses. Log VL was used in tables and regression models.

HAART use was defined as treatment with either a) two protease inhibitors; b) two nucleoside reverse transcriptase inhibitors (NRTI) with one protease inhibitors; c) two NRTI's with one non-NRTI; d) a combination of protease inhibitors and non-NRTI with NRTI; or e) three NRTI's.

Bioelectrical impedance analysis (BIA) at 50 KHz was available for 246 NFHL subjects (RJL Systems, Clinton Twp, MI, USA) and 1815 NHANES subjects (Hydra ECF/ICF BioImpedance Spectrum Analyzer Model 4200, Xitron Technologies, Inc, San Diego, CA, USA). Lean body mass was determined using a two-compartment model [34].

ALT was available for 243 of the 250 NFHL participants, and hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) were available for 233 of the 250 NFHL participants. If HCV Ab was positive, HCV RNA was obtained. Hepatitis serologic tests were not measured at the index visit for most subjects, but were assumed to be constant. ALT, and HBsAg were available for all NHANES subjects, and HCV Ab was available for 2618 NHANES subjects. Hepatitis was defined as detectable Hepatitis B surface Ag, and/or Hepatitis C RNA.

High sensitivity C-reactive protein (CRP) for NFHL participants was assayed using a turbidimetric immunoassay obtained from Wako Chemicals USA (Richmond, VA). CRP for NHANES participants was assayed using latex-enhanced nephelometry on a Behring nephelometer for quantitative CRP determination [35]. Two published studies comparing turbidimetric and nephelometric techniques in the same patients found excellent correlation between these methodologies [36;37].

Statistical Analysis

All analyses used SAS Version 9.1 (SAS Institute, Inc, Cary, NC).

For analyses within NFHL, significant differences in variables were assessed using Wilcoxon nonparametric test (if continuous), and χ^2 or Fisher exact test (if discrete). We assessed agreement using the Kappa statistic.

An upper limit of normal for serum creatinine was determined using the 95% upper confidence limit for NHANES III [38], which were then expressed as standardized creatinine values [27], resulting in cut-offs of >0.97 mg/dl (>86 μmol/L) for females and >1.16 mg/dl (>103 μmol/L) for males. The creatinine values for NFHL were not separable into tertiles because of the narrow distribution of values, therefore creatinine groups were created using sex specific cut-offs: Group 1 included women with serum creatinine values ≤ 0.53 mg/dl (≤ 47 μmol/L) and men with serum creatinine values ≤ 0.73 (≤ 65 μmol/L); Group 2 included women with serum creatinine values between 0.53 and 0.70 mg/dl (47 to 62 μmol/L), and men with values between 0.73 and 0.93 mg/dl (65–82 μmol/L); Group 3 included women with serum creatinine values ≥ 0.70 mg/dl (≥ 62 μmol/L) and men with values ≥ 0.93 mg/dl (≥ 82 μmol/L).

Several epidemiologic studies have assessed a normal range for serum cystatin C using a nephelometric assay method, with the upper limit of normal ranging from 0.65 to 0.92 mg/L [39–41]. In this study, we therefore considered a conservative cut-point of cystatin C >1.00 mg/L to be elevated. NFHL participants were stratified into tertiles of cystatin C[40].

Estimated GFR (eGFR) was categorized into less than 60, between 60 to 89, and greater than or equal to 90ml/min/1.73m^2 (<1, between 1 and 1.48, and >1.50 ml/s/1.73m^2) which

are categories consistent with staging of CKD [20]. Participants were classified into tertiles based on eGFRcys and eGFRcreat.

Analysis of NHANES 2001–2002 used appropriate weight, stratum and PSU variables in SAS Proc SurveyMeans, Proc SurveyFreq, and Proc SurveyReg, accounting for the complex sampling design of NHANES. These methods result in nationally representative means for similar persons in the non-institutionalized US adult population.

Combined analysis of the NFHL and NHANES 2001–2002 studies was accomplished by merging the two datasets (after assigning a unique stratum number for NFHL, setting NFHL participant ID to the PSU with a weight of 1, and creating a binary indicator for 'study' (1=NFHL, or 0=NHANES) as the covariate of interest), using SAS Proc Surveyreg. All multivariate analyses of the combined dataset were adjusted for age, race, sex, and BMI because of substantial differences in these covariates between the studies.

We performed an analysis of the association of hepatitis and abnormal kidney function in NFHL participants using Fisher's exact test or the χ^2 where appropriate. We obtained the common Mantel-Haenzsel relative risk after adjusting for sex, age group (20–30, 31–40, 41–50 years), BMI group (<20, 20–25, 26–30, >30), and race (White, Black, Hispanic, Other).

Results

Table 1 shows socio-demographic and clinical characteristics of NFHL and NHANES 2001–2002 subjects. Compared to NHANES subjects, NFHL subjects were slightly older, and a higher percentage were African American, mean diastolic pressures were higher, mean levels of hemoglobin and serum albumin were lower, and a higher percentage had diagnosed diabetes. There was no significant difference in Lean body mass between NFHL and NHANES participants, after adjusting for age, race, sex, and BMI (mean difference 0.75 kg, p=0.2). However, NFHL subjects had a significantly higher prevalence of liver disease than NHANES subjects, as documented by a higher mean level of ALT (43.6 mg/dl versus 26.6 mg/dl), percent with HCV antibody (36.6% versus 3.0%), or HBsAg (10.3% versus 0.3%). CRP was substantially higher in the 93 NFHL participants with available results, (2.4 mg/dl) compared to NHANES (0.29 mg/dl for males and 0.47 mg/dl for females). Mean CD4 cell count in NFHL participants was >400 cells/mm^3 and the majority had an undetectable VL.

Figure 1 compares the mean standardized serum creatinine by race and sex in NFHL and NHANES 2001–2002 subjects. Mean serum creatinine was significantly lower in NFHL than NHANES in every race-sex group except "other" women. In regression analysis, creatinine in NFHL was significantly lower than in NHANES (−0.10 mg/dL or −9μmol/L, p<0.001). After adjusting for age, race and sex, creatinine in NFHL was even lower compared with NHANES (−0.18 mg/dl or −16 μmol/L, p<0.001). In sensitivity analysis we restricted NHANES data to creatinine values ≤ 2.0 mg/dl (177 μmol/L), and found that NFHL continued to have significantly lower creatinine (−0.15 mg/dl or −13 μmol/L, p<0.001). Because of the marked difference in prevalence of hepatitis C exposure between NFHL and NHANES, and increased rates of progression to cirrhosis in HIV/HCV co-infected patients, we examined correlates of serum creatinine adjusting for age, race, sex,

ALT and HCV antibody. NFHL and HCV antibody status were both independently associated with lower levels of creatinine (−0.15 mg/dl (−13 μmol/L), p<0.001 and −0.14 mg/dl (−12 μmol/L), p<0.001, respectively).

In comparing creatinine and cystatin within the NFHL cohort, 5.2% of participants were identified with abnormal kidney function using a creatinine-based cut-off, compared with 42% using the cystatin C cut-off. The kappa statistic for agreement in identifying abnormal kidney function was poor (0.12). With eGFRcys, prevalence of eGFR less than 60 and 60–89 ml/min/1.73m^2 was 15.2% and 55%, respectively, compared to 2.4% and 20% respectively with the eGFRcreat (Figure 2). The within-individual kappa statistic showed poor agreement for eGFR <60 ml/min/1.73m2 (kappa 0.15 for eGFRcreat versus eGFRcys).

Table 2 shows the association of clinical characteristics with serum creatinine sex-specific groups and cystatin C tertiles in NFHL. Higher serum creatinine group was significantly associated with the presence of HCV antibody, history of injection drug use, and with lower CD4 cell count. Higher cystatin C tertile was more strongly associated with HCV antibody, and history of injection drug use, and was also significantly associated with lower CD4 cell count, higher log viral load, and higher ALT.

Table 3 shows demographic and laboratory factors associated with eGFRcys <60ml/min/1.73m^2 . Those with eGFRcys <60ml/min/1.73m^2 (1 ml/s/1.73m^2), were significantly more likely to have active viral hepatitis, history of injection drug use, and lower CD4 cell count, and were less likely to have an undetectable viral load.

Table 4 shows prevalence of abnormal kidney function predictors in NFHL participants with and without hepatitis. A greater proportion of participants with viral hepatitis compared to those without viral hepatitis had eGFR <60ml/min/1.73m2 (1 ml/s/1.73m^2) when determined using cystatin-based estimates of GFR but not with creatinine-based estimates.

Discussion

This is the largest study to date examining the prevalence of decreased kidney function using serum cystatin C in HIV-infected participants. Our data show two main findings. First, serum creatinine values in the HIV-infected NFHL cohort were significantly lower than those from the NHANES 2001–2002 cohort (adjusted for age, race and sex). Second, using a GFR estimating equation based on cystatin C, we observed a higher prevalence of kidney disease compared to creatinine-based estimates.

We suspect that the lower serum creatinine concentrations in the NFHL cohort than in the general population reflects decreased creatinine generation, probably related to the prevalence of liver disease in the NFHL cohort. Liver disease is a well-recognized cause of decreased creatinine generation due either to reduced muscle mass or decreased creatine synthesis [22]. While the prevalence of extensive hepatic fibrosis or cirrhosis in the NFHL cohort is unknown, hepatic fibrosis progresses more rapidly in persons co-infected with hepatitis C and HIV [42–44] and liver disease is currently the leading cause of death in NFHL.

Muscle disease related to HIV itself or HIV antiretroviral medications (especially azidothymidine) could also be responsible for decreased creatinine generation. Nucleoside reverse transcriptase inhibitors are associated with mitochondrial toxicity and myopathy [45–47]. Although we did not find decreased muscle mass in NFHL compared with NHANES, it is possible that sub-clinical myopathy occurs in asymptomatic patients on HAART, and this may be associated with decreased muscle creatine content or decreased creatinine production.

In principle, lower serum creatinine could be due to increased GFR, increased tubular secretion or increased extra-renal elimination of creatinine. However no studies have identified these factors in HIV infected patients treated with HAART.

The high prevalence of CKD defined by eGFRcys<60ml/min/1.73m2 (1 ml/s/1.73m^2) in the NFHL cohort is consistent with the high prevalence of CKD risk factors including liver disease, diabetes, and a history of injection drug use [48].

Cystatin C has been reported to be superior to creatinine for accurate estimation of GFR in a number of populations, particularly those with decreased Lean body mass or chronic liver disease [24;49–67]. Studies of cirrhotic patients that evaluated serum cystatin C and serum creatinine as filtration markers compared to measured GFR using inulin clearance [53] or 99mTc-DTPA clearance [63] found that cystatin C performed better than serum creatinine [56], consistent with the findings reported here. Although studies in cirrhotic patients have not specifically compared cystatin C-based GFR estimating equations to creatinine-based GFR estimating equations, given that serum creatinine is substantially reduced in cirrhotic patients, these equations would be expected to perform similarly poorly.

However, cystatin C has not been thoroughly evaluated as a filtration marker and preliminary evidence suggests that it may also be affected by factors other than GFR. A particular concern is inflammation. Knight et al [68] suggested that levels of cystatin C are associated with increased inflammation independent of level of kidney function (estimated by measured creatinine clearance). In our study, CRP levels in NFHL were significantly higher than in NHANES, and cystatin C levels were significantly correlated with CRP ($r=0.37$, $p<0.001$). Few studies have measured cystatin C in HIV infected persons, and these did not examine kidney function [69] or excluded persons with diabetes, hypertension or cirrhosis [11]. Inflammation may be a partial explanation for the marked difference in prevalence of decreased GFR using the two GFR estimating equations.

This study illustrates that eGFRcys can identify kidney disease in HIV-infected persons with chronic liver disease that would be undetected by serum creatinine-based measurements. Among HIV infected subjects with and without chronic hepatitis, for example, the eGFRcreat identified kidney impairment in only 5% and 1% respectively, not showing the increased prevalence that is expected with chronic hepatitis. In contrast the eGFRcys identified kidney impairment in 7% of HIV-infected subjects without hepatitis, which increased to 30% in HIV-infected subjects with hepatitis.

A strength of this study is use of serum creatinine and cystatin C values calibrated to the same instrument used for development of the respective estimating equations. In addition,

we were able to assess lean body mass, and to look at other variables associated with risk of abnormal kidney function. This is the first study comparing lean body mass of HIV infected persons taking HAART versus a similarly aged national cohort.

The primary limitation is that we did not use a gold standard method for determination of GFR. We are relying on serum creatinine and cystatin C-based GFR estimating equations in a population in whom the accuracy of these equations is unknown [70]. In addition, NFHL did not collect urine samples for proteinuria or renal biopsy, and this analysis had only one creatinine and cystatin C sample per individual. Thus we could not make a formal diagnosis of CKD, which requires evidence of kidney damage or eGFR <60 ml/min/1.73m^2 (1 ml/s/1.73m^2) that persists for three or more months [20].

These data suggest that CKD may be more prevalent in HIV-infected patients than is currently believed, and that cystatin C may be a better marker of abnormal kidney function in the HIV population, particularly those with chronic viral hepatitis co-infection [71]. Both have important implications for care of HIV-infected patients. Studies using gold-standard exogenous clearance methods for measuring GFR are required for more definitive answers.

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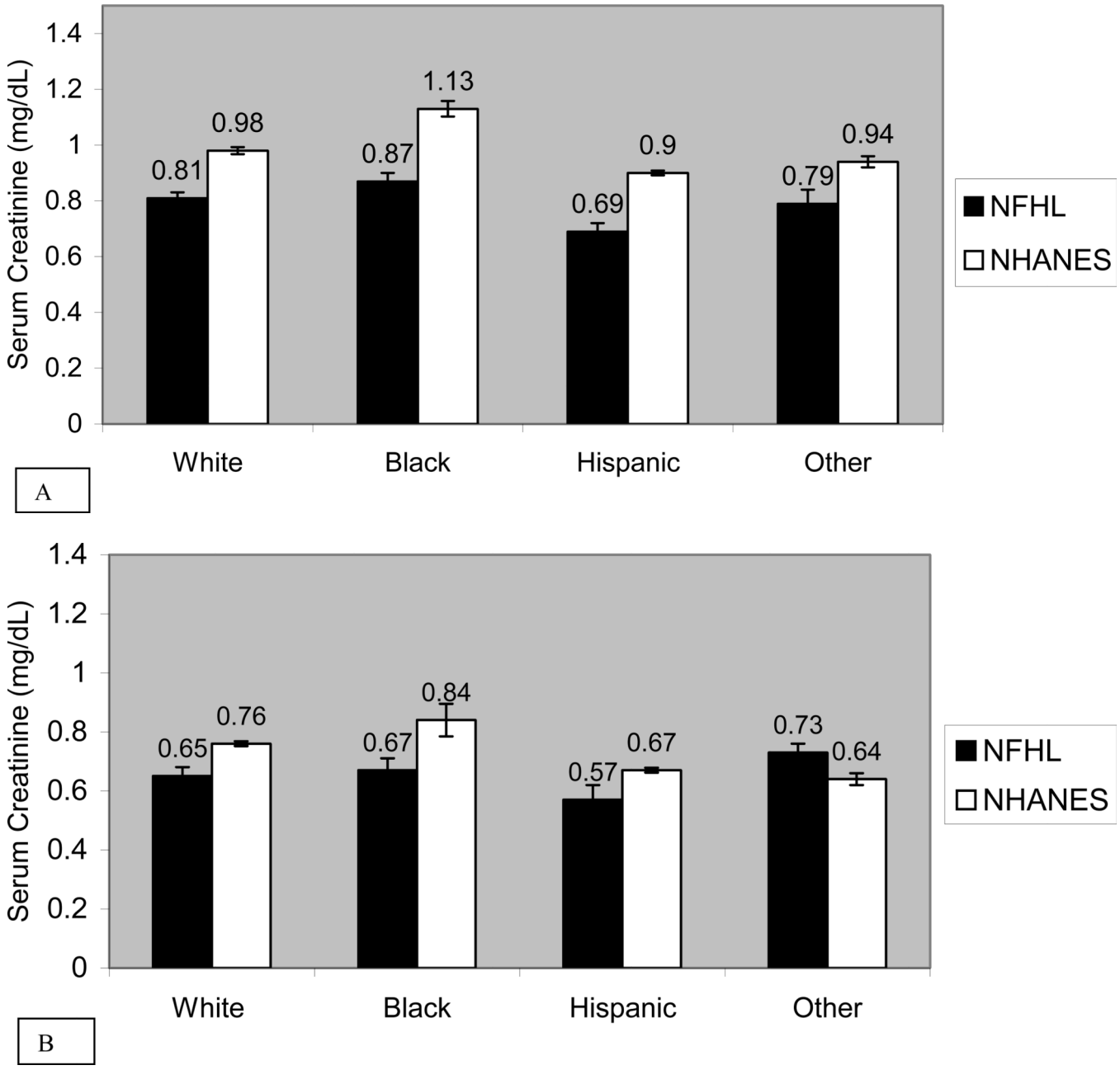

Figure 1. Mean Serum Creatinine in Men and Women in NFHL and NHANES 2001–2002

Unadjusted mean serum creatinine and standard error of the mean (SEM) bars in NFHL and NHANES 2001–2002 subjects, stratified by race for men (panel A) and women (panel B). Units for creatinine are mg/dl. Abbreviations used in this figure include: NFHL (Nutrition for Healthy Living) and NHANES (National Health and Nutrition Examination Survey 2001–2002)

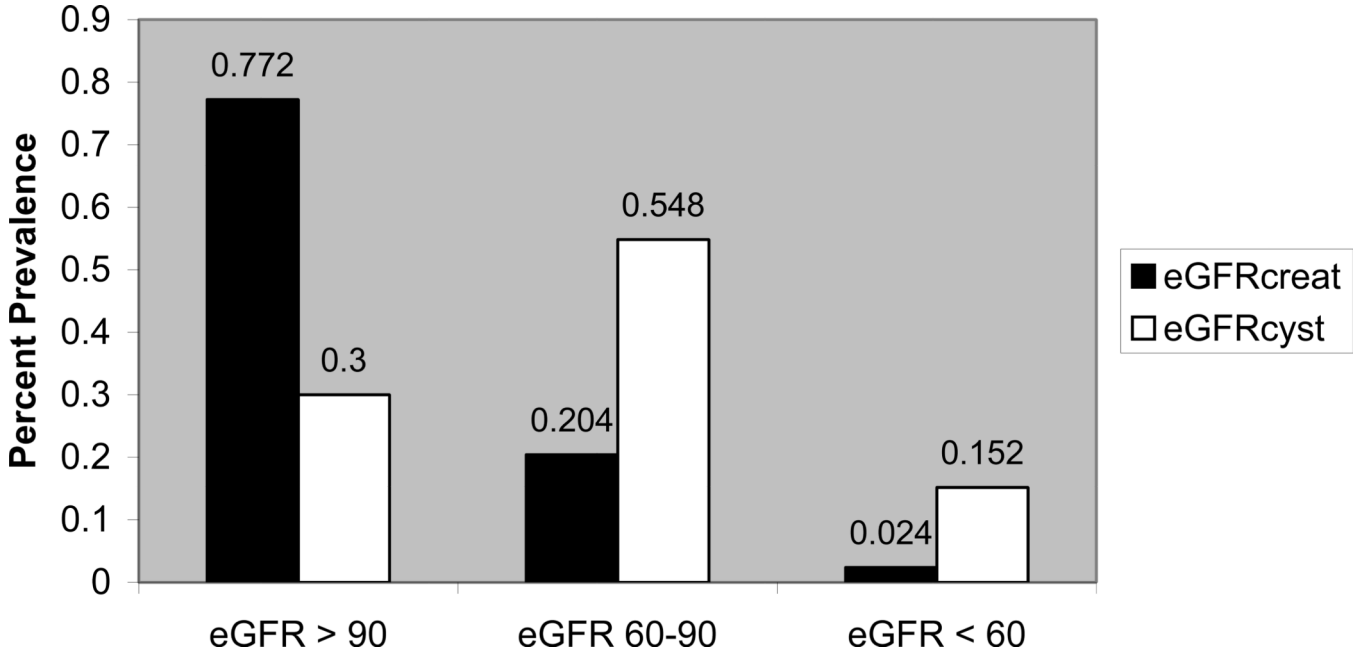

Figure 2. Percent Prevalence of Kidney Disease in NFHL by eGFRcreat and eGFRcystatin

Percent prevalence of estimated GFR >90, 60–89, and <60 ml/min/1.73m2 in NFHL subjects as assessed by the Modification of Diet in Renal Disease (MDRD) GFR estimating equation (eGFRcreat), and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin GFR estimating equation (eGFRcys). Abbreviations used in this figure include: NFHL (Nutrition for Healthy Living), eGFR (estimated glomerular filtration rate).

Table 1

Demographic, Laboratory and Examination Characteristics in NFHL and NHANES given as mean (SEM)*

	NFHL (HIV+)			NHANES 2001–2002†		
Mean (SEM)	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**
	(N=250)	**(N= 174)**	**(N=76)**	**(N=2628)**	**(N=1202)**	**(N=1426)**
Age (years)	41.8 (0.3)	42.0 (0.4)	41.3 (0.6)	35.3 (0.3)	35.9 (0.3)	34.8 (0.4)
Race (%):African American	31.6	25.9	44.7	11.5	10.2	12.7
White	52.8	60.3	35.5	67.7	69.4	66.1
Hispanic	10.4	9.2	13.2	15.8	15.8	15.9
Other	5.2	4.6	6.6	5.0	4.7	5.3
CD4 cell count (cells/mm^3)	442 (17)	434 (20)	461 (36)	----	----	----
% Undetectable viral load	67.2	67.1	67.6	----	----	----
BMI (kg/m^2)	26.5 (0.3)	25.8 (0.3)	28.1 (0.9)	27.7 (0.16)	27.7 (0.20)	27.7 (0.24)
Creatinine (mg/dl)	0.77 (0.01)	0.81 (0.02)	0.66 (0.02)	0.86 (0.01)	0.98 (0.01)	0.75 (0.01)
Cystatin C (mg/L)	1.03 (0.02)	1.04 (0.02)	1.00 (0.03)	----	----	----
eGFRcreat (ml/min/1.73m^2)	120.0 (2.8)	120.9 (3.7)	117.5 (4.1)	96.0 (1.1)	94.3 (1.6)	97.7 (1.07)
eGFRcys (ml/min/1.73m^2)	79.3 (1.2)	77.6 (1.3)	83.3 (2.5)	----	----	----
Lean Body Mass (kg)	57.6 (0.7)	62.1 (0.6)	47.3 (1.0)	53.8 (0.44)	62.5 (0.4)	45.2 (0.4)
ALT (IU/L)	43.6 (2.4)	48.6 (3.1)	31.6 (3.3)	26.6 (1.0)	31.4 (0.6)	21.9 (1.9)
HCV Antibody Positive ‡ (%)	38.6	36.3	43.8	3.0	3.8	2.3
HBsAg (%)	10.3	10.0	11.0	0.25	0.46	0.04
IDU Ever§ (%)	31.6	29.3	36.8	----	----	----
Systolic Blood Pressure (mm Hg) ‖	117 (1.0)	120 (1.1)	111 (2.1)	116 (0.4)	120 (0.6)	113 (0.4)
Diastolic Blood Pressure (mm Hg) ¶	76 (0.7)	76 (0.8)	74 (1.3)	72 (0.4)	74 (0.4)	70 (0.5)
Diabetes Mellitus# (%)	6.4	4.6	10.5	3.3	3.7	2.9
Albumin** (mg/dl)	3.94 (0.03)	3.99 (0.03)	3.84 (0.05)	4.30 (0.01)	4.42 (0.01)	4.18 (0.01)
Hemoglobin (g/dl) ††	14.0 (0.1)	14.5 (0.1)	12.7 (0.2)	14.5 (0.1)	15.5 (0.1)	13.5 (0.1)
Hematocrit‡‡	41.0 (0.3)	42.3 (0.3)	38.1 (0.5)	42.5 (0.2)	45.7 (0.2)	39.5 (0.2)
CRP (mg/dl)	2.39 (0.28)	2.40 (0.34)	2.37 (0.52)	0.38 (0.02)	0.29 (0.02)	0.47 (0.03)

Abbreviations used in this table: Nutrition for Healthy Living (NFHL), National Health and Nutrition Survey 2001–2002 (NHANES), standard error of the mean (SEM), body mass index (BMI), estimated glomerular filtration rate based on the Modification of Diet in Renal Disease estimating equation (eGFRcreat), estimated GFR based on the U01 study cystatin estimating equation (eGFRcys), hepatitis C virus (HCV), hepatitis B surface antigen (HBSAg), alanine aminotransferase (ALT), injection drug use (IDU), and C-reactive protein (CRP).

To convert to SI units: for creatinine mg/dl to μmol/L, multiply value by 88.4; for albumin g/dL to g/L multiply value by 10; for hemoglobin g/dL to g/L, multiply value by 10.

[*] Values represent mean and standard error of the mean (SEM) unless otherwise noted.

[†] N= Actual number of Nutrition for Healthy Living (NFHL) and National Health and Nutrition Survey 2001–2002 (NHANES) participants included in this analysis. All other information for NHANES has been derived using the proper weight, and accounting for the complex sampling design of NHANES 2001–2002, and thus should constitute nationally representative data for non-institutionalized persons in the US who would meet the entry criteria of this study.

[‡] Percent of participants with detectable hepatitis C virus (HCV) antibody.

[§] A history of ever using injection drugs either at baseline or at any study visit.

[//] Systolic blood pressure (mm Hg) was available for 173 men and 71 women in NFHL, and for 1159 men and 1359 women in NHANES

[¶] Diastolic blood pressure (mm Hg) was available for 173 men and 71 women in NFHL, and for 1159 men and 1359 women in NHANES

[#] History of diabetes was determined by self-report of health professional diagnosed diabetes on the NFHL or the NHANES questionnaire.

[**] Albumin was available for 170 men and 69 women in NFHL, and for 1202 men and 1426 women in NHANES

[††] Hemoglobin was available for 174 men and 75 women in NFHL, and for 1201 men and 1425 women in NHANES

[‡‡] Hematocrit was available for 174 men and 75 women in NFHL, and for 1201 men and 1425 women in NHANES

Table 2

Association of Demographic, and Laboratory Characteristics with Cystatin C Tertiles and Creatinine Groups

	Cystatin C Tertiles*				Creatinine Groups†			
Mean (SD)‡	**Tertile 1 <0.88mg/L (N=80)**	**Tertile 2 88-1.05mg/L (N=85)**	**Tertile 3 ≥1.06 mg/L (N=85)**	**P-value**	**Group1 (N=102)**	**Group2 (N=89)**	**Group3 (N=59)**	**P-value**
Age (years)	41.6 (4.8)	40.8 (5.5)	43.0 (5.0)	0.02	41.7 (5.6)	41.0 (5.0)	43.1 (4.4)	0.07
% Female	44	22	26	0.006	24	28	46	0.01
Race(%):								
African American	43	31	22	0.1	27	30	41	0.03
White	41	55	61		52	55	51	
Hispanic	10	8	13		18	8	2	
Other	6	6	4		3	7	7	
BMI (kg/m^2)	26.8 (6.8)	27.1 (4.8)	25.5 (4.1)	0.2	26.3 (5.1)	26.7 (5.8)	26.5 (5.3)	0.7
Creatinine (mg/dl)	0.68 (0.17)	0.76 (0.18)	0.85 (0.27)	0.006	0.60 (0.12)	0.80 (0.12)	1.00 (0.23)	<0.0001
Cystatin C (mg/L)	0.80 (0.07)	0.97 (0.05)	1.30 (0.26)	<0.0001	0.97 (0.19)	0.99 (0.20)	1.18 (0.36)	<0.0001
eGFRcreat(ml/min/1.73m^2)	131 (37)	122 (46)	108 (49)	<0.0001	155 (49)	105 (12)	81 (15)	<0.0001
eGFRcys (ml/min/1.73m^2)	101 (11)	80 (5)	58 (10)	<0.0001	83 (18)	81 (19)	69 (20)	<0.0001
HCVAntibody (%)	20.6	36.4	56.6	<0.0001	39.0	29.6	50.9	0.04
ALT (IU/L)	37 (30)	40 (33)	53 (47)	0.001	45 (42)	42 (36)	44 (34)	0.4
CD4 cell count (cells/mm^3)	522 (262)	434 (228)	373 (303)	0.0002	446 (272)	489 (299)	367 (208)	0.05
Log_{10} viral load (copies/ml)	2.48 (0.45)	2.74 (0.75)	3.25 (1.21)	<0.0001	2.85 (0.95)	2.80 (0.89)	2.81 (0.94)	1.0
% undetectable viral load	84	66	52	0.0001	68	69	66	1.0
IDU ever (%)	17.5	24.7	51.8	<0.0001	30	25	44	0.04
Fat Free Mass (kg)	56.5 (11.3)	59.5 (10.5)	56.7 (10.3)	0.1	58.1 (10.5)	58.9 (11.3)	54.6 (9.9)	0.9
Fat Free Mass Percent	74.9 (11.0)	75.4 (10.7)	75.5 (10.3)	1.0	75.3 (10.5)	76.6 (11.0)	73.1 (10.2)	0.1
Years HIV Positive	9.0 (4.8)	8.7 (4.1)	10.0 (4.3)	0.1	9.0 (4.4)	8.9 (4.6)	10.3 (4.3)	0.2
Systolic Blood Pressure	116 (14)	119 (15)	118 (18)	0.7	118 (14)	117 (15)	118 (19)	0.8
Diastolic Blood Pressure	75 (10)	76 (8)	76 (12)	0.7	74 (8)	76 (11)	77 (13)	0.5
Albumin	4.08 (0.31)	3.96 (0.36)	3.80 (0.49)	0.0001	3.93 (0.44)	3.94 (0.36)	3.96 (0.45)	0.9
Hemoglobin	13.9 (1.6)	14.1 (1.8)	13.9 (1.8)	0.6	14.0 (1.7)	14.1 (1.7)	13.7 (1.9)	0. 5
% on Tenofovir	10.0	14.1	15.3	0.6	9	13	20	0.1

Mean (SD)‡	Cystatin C Tertiles*				Creatinine Groups†			
	Tertile 1 <0.88mg/L (N=80)	Tertile 2 88-1.05mg/L (N=85)	Tertile 3 ≥1.06 mg/L (N=85)	P-value	Group1 (N=102)	Group2 (N=89)	Group3 (N=59)	P-value
% on Indinavir	12.5	7.1	10.6	0.5	9	13	7	0.4
CRP§	2.23 (2.56)	1.98 (1.80)	3.23 (3.83)	0.4	2.46 (2.27)	2.06 (2.60)	2.70 (3.44)	0.3

Abbreviations used in this table: standard deviation (SD), body mass index (BMI), estimated glomerular filtration rate based on the Modification of Diet in Renal Disease estimating equation (eGFRcreat), estimated GFR based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin estimating equation (eGFRcys), hepatitis C virus (HCV), hepatitis B surface antigen (HBSAg), alanine aminotransferase (ALT), injection drug use (IDU), human immunodeficiency virus (HIV), C-reactive protein (CRP).

To convert to SI units: for creatinine mg/dl to μmol/L, multiply value by 88.4; for albumin g/dL to g/L multiply value by 10; for hemoglobin g/dL to g/L, multiply value by 10.

*Normal range for cystatin C is considered to be <1.00. Cystatin C was normally distributed with a mean (SD) of 1.03 (0.26) mg/L and range 0.62–2.42 mg/L.

†Creatinine groups were created using sex specific cut-offs of standardized creatinine: Group 1 had creatinine ≤ 0.53 if female and ≤ 0.73 if male; Group 2 had creatinine > 0.53 and <0.7 if female, and >0.73 and <0.93 if male; Group 3 had creatinine ≥ 0.7 if female and ≥ 0.93 if male. These groups are not tertiles but come as close to tertiles as possible given the resolution and spread of the data.

‡Values represent mean (SD) unless otherwise indicated.

§Of those in cystatin tertile 1, 2, and 3, the number of participants with available CRP was 28, 40, and 25 respectively. Of those in creatinine groups 1, 2, and 3, the number of participants with available CRP was 36, 32,and 25 respectively.

Table 3

Association of Demographic, and Laboratory Characteristics with eGFRcys <60 ml/min/1.73m^2

Mean (SD)*	eGFRcys ≥60 (N=212)	eGFRcys <60 (N=38)	P-value
Creatinine (mg/dl)	0.74 (0.19)	0.90 (0.32)	0.003
Cystatin C (mg/L)	0.94 (0.14)	1.50 (0.27)	<0.0001
eGFRcreat (ml/min/1.73m^2)	123 (40)	105 (64)	<0.0001
eGFRcys (ml/min/1.73m^2)	85 (15)	49 (8)	<0.0001
Age (years)	41.4 (5.2)	44.1 (4.7)	0.05
HCVAntibody (%)	33.9	63.2	0.0007
ALT (IU/L) Mean (SD)	40 (31)	62 (61)	0.003
Active Viral Hepatitis†	33.3	73.7	<0.0001
Albumin	3.99 (0.40)	3.67 (0.41)	<0.0001
CD4 cell count (cells/mm^3)	466 (271)	311 (235)	0.006
Log viral load (copies/ml)	2.74 (0.80)	3.30 (1.33)	0.009
% undetectable log viral load	70.3	52.6	0.03
IDU ever (%)	26.4	60.5	<0.0001
Fat Free Mass (kg)	58.3 (10.8)	53.3 (9.5)	0.01
Hemoglobin	14.1 (1.7)	13.5 (1.8)	0.04

Abbreviations used in this table: standard deviation (SD), estimated glomerular filtration rate based on the Modification of Diet in Renal Disease estimating equation (eGFRcreat), estimated GFR based on the U01 study cystatin estimating equation (eGFRcys), hepatitis C virus (HCV), hepatitis B surface antigen (HBSAg), alanine aminotransferase (ALT), injection drug use (IDU).

To convert to SI units: for creatinine mg/dl to μmol/L, multiply value by 88.4; for albumin g/dL to g/L multiply value by 10; for hemoglobin g/dL to g/L, multiply value by 10.

None of the following covariates were significantly associated with eGFRcys < 60 ml/min/1.73m2: Race, sex, BMI, fat-free mass percent, years of known HIV infection, systolic or diastolic blood pressure , % taking tenofovir, % taking indinavir, or CRP.

*Values represent mean and standard deviation (SD) unless otherwise indicated. P-values are from Wilcoxon models.

†Participants with active viral hepatitis had either detectable hepatitis C virus (HCV) RNA or hepatitis B virus surface antigen (HBSAg). Hepatitis testing was available for 233 participants.

Table 4

N (%) of NFHL Participants with Abnormal Kidney Parameters by Hepatitis Status*

	Hepatitis (N=93)	No Hepatitis (N=140)	Mantel-Haentzel RR† (95% CI)
Elevated Creatinine‡	9 (10%)	4 (3%)	2.54 (0.91, 7.09)
Elevated Cystatin C‡	57 (61%)	43 (31%)	2.32 (1.59, 3.39)
eGFRcreat <60	5 (5%)	1 (1%)	5.41 (0.94, 31.07)
eGFRcys <60	28 (30%)	10 (7%)	4.04 (1.75, 9.33)

Abbreviations used in this table: Nutrition for Healthy Living study (NFHL), National Health and Nutrition Examination Survey 2001–2002 (NHANES), estimated glomerular filtration rate based on the Modification of Diet in Renal Disease estimating equation (eGFRcreat), estimated GFR based on the U01 study cystatin estimating equation (eGFRcys), relative risk (RR), body mass index (BMI).

*Two hundred thirty three NFHL subjects had hepatitis serology (160 men and 73 women). Hepatitis was defined as either detectable Hepatitis B surface Ag, or Hepatitis C RNA. Of those with hepatitis, 28 (30%) were female. Of those without hepatitis, 48 (34%) were female.

†This RR is a Mantel-Haenszel relative risk of kidney disease in those with viral hepatitis versus without viral hepatitis, after stratification by sex, age group (20–30, 31–40, 41–50 years), BMI group (<20, 20–25, 26–30, >30), and race (White, Black, Hispanic, Other).

‡Elevated creatinine: Cr > 0.97 mg/dl (86μmol/L) if female, or 1.16 mg/dl (103 μmol/L)if male. Elevated cystatin C: Cystatin C > 1.00 mg/L for both sexes