Relationship between Hepatitis C and Chronic Kidney Disease: Results from the Third National Health and Nutrition Examination Survey

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Previous research supports an association between hepatitis C virus (HCV) infection and glomerulonephritis. However, little is known about the association between HCV and chronic kidney disease. The cross-sectional association between prevalent hepatitis C seropositivity and albuminuria and estimated GFR (eGFR), respectively, was examined among 15,029 participants in the Third National Health and Nutrition Examination Survey (NHANES III). In the multivariate analysis, we noted an age-dependent association between HCV seropositivity and albuminuria (adjusted odds ratios and 95% confidence intervals 0.83, 0.39 to 1.75 for ages 20 to 39; 1.84, 1.00 to 3.37 for ages 40 to 59; 2.47, 1.27 to 4.80 for ≥60 yr of age). There was no significant association observed for hepatitis C seropositivity and low eGFR (<60 ml/min per 1.73 m²; adjusted odds ratios and 95% confidence interval for all ages 0.89, 0.49 to 1.62). Among a representative sample of the US population, hepatitis C is independently associated with albuminuria among adults over the age of 40; however, it does not seem to be significantly associated with a low eGFR in this population-based cross-sectional analysis.

An estimated 4 million Americans have been exposed to the hepatitis C virus (HCV), representing approximately 2% of the US population (1). Although the primary burden of disease that is associated with chronic hepatitis C is liver related (liver fibrosis, cirrhosis, and hepatocellular carcinoma), other organ systems may be involved. In the kidney, HCV seems to be most strongly associated with membranoproliferative glomerulonephritis (MPGN; both with and without cryoglobulins) and membranous glomerulonephritis, although other types of glomerulonephritis also have been described (2–4). The prevalence of HCV seropositivity among case series of patients with MPGN is approximately 10-fold higher than the national prevalence for HCV (2,5–7). In addition, the prevalence of MPGN among both live cohorts and autopsy series of HCV-infected individuals seems to be substantially higher than for the general population (8,9).

Some authors have suggested that screening for proteinuria and creatinine clearance may be indicated among patients with chronic HCV (10,11). However, relatively little information is available on the prevalence of chronic kidney disease (CKD) among individuals with HCV to support this practice (12). Although the prevalence of HCV among individuals with

ESRD is much higher than for the general population, it is unclear to what extent this reflects an increased risk for viral exposure among people with advanced kidney disease (through blood transfusions and nosocomial transmission) or alternatively a greater incidence and rapid progression of renal disease in patients with HCV (13–15).

We used cross-sectional data from the Third National Health and Nutrition Examination Survey (NHANES III) to compare the prevalence of albuminuria and low estimated GFR (eGFR) among a representative sample of the US population with and without HCV. We hypothesized that HCV would be associated with a higher prevalence of both albuminuria and low eGFR.

Materials and Methods

Survey Design and Study Sample

NHANES III was conducted from 1988 to 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention and has been fully described previously (16,17). Briefly, this survey uses a complex multistage, stratified, and clustered probability sample of the civilian, noninstitutionalized population age 2 mo and older. Interview, examination, and laboratory data were collected on approximately 34,000 individuals sampled from 89 randomly selected locations throughout the United States.

Participants in NHANES III were included in this analysis when they were ≥20 yr of age; had completed a standardized interview and physical examination; and had complete, nonindeterminate data on HCV serum antibody testing, a spot urine albumin to creatinine ratio, and serum creatinine for use in the abbreviated Modification of Diet in Renal Disease formula (18). Of 18,825 individuals who were at least 20 yr of age, 16,573 had laboratory and physical examination data avail-

able, 15,040 of whom met study entry criteria as defined above. In addition, because the focus of this study is on the association of HCV with moderate to severe CKD rather than established renal failure, we excluded 11 participants with an eGFR <15 ml/min per 1.73 m^2, leaving a final sample of 15,029. The institutional review board of the Centers for Disease Control and Prevention approved NHANES III, and all participants provided their written consent to participate. The study described herein was granted exempt status by the University of California at San Francisco institutional review board.

Study Variables

The primary independent variable was exposure to HCV, as determined by presence of antibody to HCV (anti-HCV Ab). Anti-HCV Ab was measured using a second-generation enzyme immunoassay test (Abbott Laboratories, Chicago, IL). Positive specimens were tested in duplicate and then retested using an additional assay (MATRIX; Abbott Laboratories), and specimens that were positive according to all three tests were reported as positive. Indeterminate tests were excluded from the analysis. Specimens that were HCV Ab positive were tested for HCV RNA using reverse transcriptase–PCR amplification of the 5' noncoding region. Individuals with a positive HCV antibody test and detectable HCV RNA were classified as having chronic HCV. In a secondary analysis, we measured the association of chronic HCV with each dependent variable.

The dependent variables of interest were presence of albuminuria and low eGFR. We examined eGFR as both a continuous and a dichotomous variable using a threshold value of <60 ml/min per 1.73 m^2 to define low eGFR. There was a mild right skewness in the distribution of eGFR values in the study sample because some patients had very inflated eGFR values. We assigned an eGFR value of 200 to all individuals with calculated eGFR values >200. We repeated the analyses using the natural logarithm of eGFR as the dependent variable to correct for skewness; however, results did not differ significantly, and therefore we present results for the untransformed variable for the sake of clarity. These variables were chosen on the basis of the current National Kidney Foundation guidelines' definition of CKD as kidney damage (most frequently detected as persistent albuminuria) or decreased kidney function (eGFR <60 ml/min per 1.73 m^2) for 3 mo or more (18). GFR was calculated using the abbreviated Modification of Diet in Renal Disease equation that is based on serum creatinine, age, gender, and race (18). Creatinine measurements were calibrated to the Cleveland Clinic laboratory by subtracting 0.23 mg/dl (19). Albuminuria was determined on the basis of spot urine albumin (μg/ml)/creatinine (mg/ml) ratios. Albuminuria was defined as $\geq$17 μg/mg for women and $\geq$25 μg/mg for men (18).

Multivariable analyses were adjusted for the following covariates: Age, gender, race/ethnicity, educational status, smoking status, diabetes, and hypertension. Race/ethnicity was divided into four categories: non-Hispanic white, non-Hispanic black, Mexican-American, and other. Age was stratified into three groups: 20 to 39, 40 to 59, and $\geq$60 yr of age. Educational status was dichotomized at the 12th-grade level. Participants were classified as current or nonsmokers. They were defined as having diabetes when a doctor had ever told them that they had diabetes or when they reported taking medication for diabetes. Participants were considered to have hypertension when they reported having been told by a doctor that they had high BP, were on medication for high BP, or their mean examination BP was >140/90 mmHg.

Statistical Analyses

We performed cross-sectional analyses to examine the association between prevalent HCV seropositivity and prevalent albuminuria and

eGFR, respectively. All statistical analyses were conducted using Stata 8.2 (Stata Corp., College Station, TX) and incorporated sample weights to accommodate the complex survey design. NHANES sampling weights were inflated so that the sums of the weights for respondents with nonmissing serum creatinine, urine creatinine, urine albumin, and hepatitis C Ab results within subgroups defined by NHANES stratum, age, gender, and race were equal to the sum for all respondents in the subgroup. This re-weighting procedure provides approximately unbiased estimates of population parameters under the assumption that test values were missing at random within each subgroup. We compared characteristics of patients with and without hepatitis C Ab using general descriptive statistics that were weighted for the complex survey design. In the primary analyses, we examined the univariate and multivariate associations of HCV seropositivity with each dependent variable using survey logistic regression for the dichotomous variables (albuminuria and eGFR <60 ml/min per 1.73 m^2) and survey linear regression for the continuous variable eGFR. We used full models for all multivariate analyses, adjusting for all covariates that had been used in the descriptive analysis (age, gender, race/ethnicity, educational status, smoking status, diabetes, and hypertension), because they were hypothesized to be possible confounders. In secondary analyses, we also examined the association of chronic HCV infection with the same dependent variables. We tested for interactions with age, race, and diabetes in each model. To determine the impact of cirrhosis on study results, we repeated the primary analysis in a subset of participants with platelet counts >130 × 10^3/μl ($n = 14,900$) to exclude participants with cirrhosis. This index has been found to have acceptable sensitivity and specificity (91 and 88%, respectively) for diagnosing cirrhosis among patients with chronic liver disease as a result of hepatitis C (20).

Results

Among the 15,029 participants in this analysis, 366 individuals were positive for HCV Ab (estimated prevalence 2.2%; 95% confidence interval [CI] 1.7 to 2.8%). This is similar to the estimated national prevalence (1.8%), based on the complete NHANES III cohort (1). Eighty percent of individuals who were seropositive to HCV had detectable virus (i.e., chronic infection). In our sample, individuals with hepatitis C seropositivity were more likely to be male, nonwhite, aged 30 to 49, smokers, and non–high school graduates ($P < 0.05$; Table 1). There were no statistically significant differences in the prevalence of diabetes and hypertension by HCV Ab status.

Albuminuria

The prevalence of albuminuria increased with age among both seropositive and seronegative individuals (Figure 1). In younger participants, the prevalence of albuminuria was similar among those who were seropositive and seronegative; however, among older participants (age $\geq$ 40), the prevalence of albuminuria was higher among seropositive participants. The most striking difference observed was among individuals who were older than 60, in whom 46% (95% CI 32 to 60%) of HCV-seropositive individuals had albuminuria compared with only 24% (95% CI 22 to 26%) of those without HCV antibody.

Because of a significant interaction between HCV and age for albuminuria (overall $P = 0.004$ for interaction), we present multivariate results stratified by age group (Table 2). Hepatitis C seropositivity was associated with albuminuria only among those who were older than 40 yr, and the association was

Table 1. Participant characteristics by HCV seropositivity[a]

	HCV Antibody		P[b]
	Negative (%)	Positive (%)	
Male	47	67	<0.01
Race			
white	76	61	<0.01
black	11	20	
Mexican-Hispanic	5	6	
other	8	13	
Age (yr)			
20 to 39	45	57	<0.01
40 to 59	32	34	
≥60	22	9	
Diabetes	5	5	0.76
Hypertension	31	27	0.28
Current smoker	28	59	<0.01
High school graduate	74	57	<0.01

[a]HCV, hepatitis C virus.
[b]Pearson $\chi 2$ test.

strongest for those who were 60 yr and older ($P = 0.01$ for trend across age categories). An age interaction also was present in analyses of chronic HCV. Among people who were aged 20 to 39, chronic HCV was negatively associated with albuminuria, whereas in individuals who were ≥60 yr of age, chronic HCV was positively associated. There were no significant interactions of race and diabetes with either HCV seropositivity or chronic HCV for predicting albuminuria.

eGFR

Mean serum creatinine did not differ between people with and without HCV Ab (0.84 mg/dl [95% CI 0.83 to 0.85] for HCV seropositive *versus* 0.83 mg/dl [95% CI 0.80 to 0.86] for HCV seronegative). The mean eGFR was 100 ml/min per 1.73 m^2 (95% CI 99 to 101) for participants who were HCV Ab negative compared with 110 ml/min per 1.73 m^2 (95% CI 106 to 114) for individuals who were HCV Ab positive. After adjustment for confounders, participants with HCV seropositivity were found to have a mean eGFR that was on average 5 ml/min per 1.73 m^2 higher than those without HCV (95% CI 1 to 9; $P = 0.014$). The prevalence of low eGFR, although generally low in both groups, was higher among participants who were seronegative for HCV than among HCV-seropositive individuals (4.3% [95% CI 3.7 to 4.9%] of individuals without anti-HCV Ab had eGFR <60 ml/min per 1.73 m^2 *versus* 2.0% [95% CI 1.1 to 3.6%] of individuals with anti-HCV Ab; Figure 2). In univariate analysis, HCV was negatively associated with low eGFR, but this association was no longer statistically significant after adjustment for confounders (Table 2). There were no significant interactions ($P < 0.1$) between HCV seropositivity and chronic infection and age, race, or diabetes for predicting low eGFR.

Sensitivity Analyses

To determine whether the presence of cirrhosis among patients with HCV may have biased our results, we conducted a

sensitivity analysis in a subset of individuals with normal platelets (>130 × 10^3/μl), who therefore were unlikely to have cirrhosis. In this group, albuminuria remained associated with HCV Ab among people who were 40 yr or older; adjusted odds ratios (OR) and 95% CI for HCV were 0.85 (0.40 to 1.79) for 20 to 39, 1.79 (0.98 to 3.25) for 40 to 59, and 2.08 (0.92 to 4.73) for ≥60 yr. Likewise, the unadjusted odds of low eGFR were significantly lower among individuals with HCV seropositivity (OR 0.38; 95% CI 0.18 to 0.81), but this finding was no longer significant after adjustment for confounders (OR 0.88; 95% CI 0.42 to 1.85).

Discussion

In a nationally representative sample of the US civilian non-institutionalized population, we found an independent association between albuminuria and HCV seropositivity among adults who were older than 40 yr. The association was most pronounced for people who were older than 60 yr, among whom almost half of those with HCV Ab had albuminuria, compared with approximately one fourth of those without Ab to HCV. In contrast, HCV-seropositive individuals seemed to have a higher mean eGFR and were less likely than those without HCV to have an eGFR <60 ml/min per 1.73 m^2, although the latter association did not reach statistical significance after adjustment for potential confounders.

Our findings differ from a previously published study using NHANES III data that examined the association between HCV and microalbuminuria as a component of the metabolic syndrome (21). These authors reported an association between albuminuria and HCV for the entire adult sample but did not use sample weights to account for the complex survey design (therefore biasing their point estimates and CI [22]) and did not perform any stratified analysis to see how the association varied across age groups (21). We observed an association between HCV seropositivity and albuminuria only for adults who were older than 40 yr.

An age-dependent association also has been reported for HCV and diabetes (23,24). However, adjustment for diabetes in the multivariate analysis did not alter results, suggesting that HCV and albuminuria are associated independently. It is plausible that nonhepatic manifestations of HCV, such as albuminuria and diabetes, develop after many years of chronic infection. Case series of patients with MPGN and HCV describe the average age to be 50 yr or older (2,6). Although the mechanism of HCV-related renal disease is uncertain, research suggests that glomerular injury results from deposition of circulating immune complexes that contain hepatitis C Ab, antigens, and complement (11). It also could be a result of accelerated atherosclerosis among individuals with HCV, which has been suggested in some studies (25–29).

In this analysis, it seemed that whereas albuminuria was a common finding among older individuals with HCV, low eGFR was no more common in this group than in the general population. Indeed, when mean eGFR was compared between participants with and without HCV seropositivity, seropositive individuals tended to have a higher mean eGFR, even after controlling for potential confounders. This unexpected finding
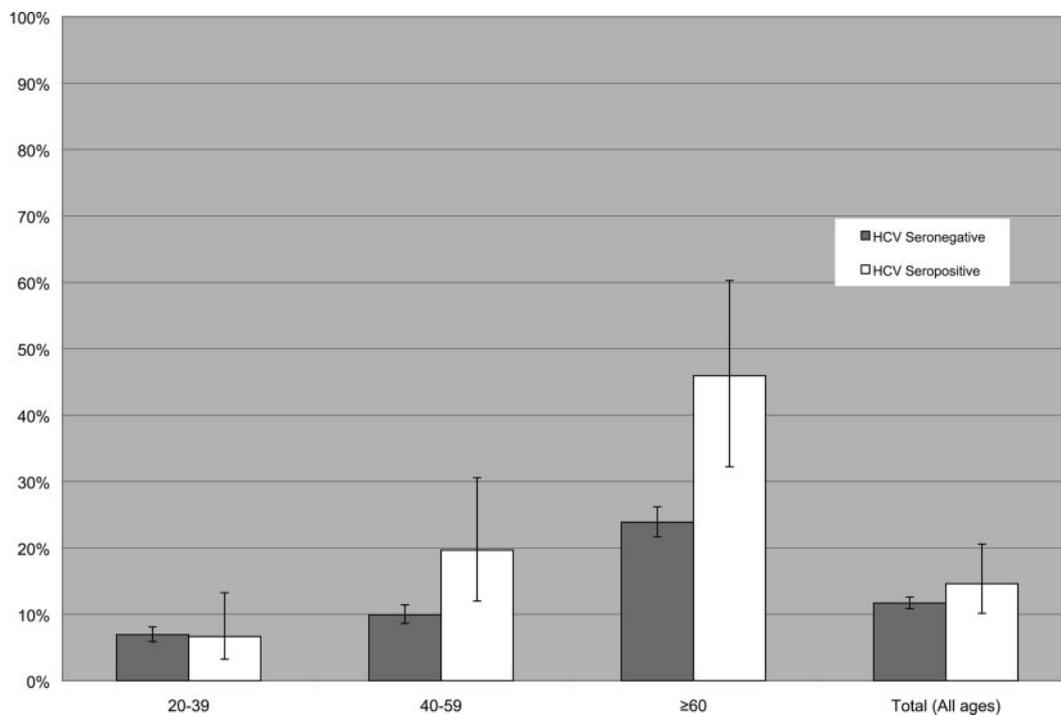
Figure 1. Prevalence of albuminuria by age and hepatitis C seropositivity.

Table 2. Association between hepatitis C and albuminuria and low eGFR[a]

HCV Seropositivity as Predictor	Unadjusted OR	95% CI	P	Adjusted OR[b]	95% CI	P
Albuminuria						
age						
20 to 39	0.54	0.26 to 1.14	0.1	0.83	0.39 to 1.75	0.62
40 to 59	1.85	1.02 to 3.34	0.04	1.84	1.00 to 3.37	0.05
≥60	6.41	3.56 to 11.54	<0.01	2.47	1.27 to 4.80	0.01
all ages	1.29	0.86 to 1.93	0.2	1.38	0.91 to 2.07	0.12
Low eGFR[c]						
all ages	0.45	0.24 to 0.85	0.02	0.89	0.49 to 1.62	0.7

Chronic HCV as Predictor	Unadjusted OR	95% CI	P	Adjusted OR[b]	95% CI	P
Albuminuria						
age						
20 to 39	0.23	0.10 to 0.52	<0.01	0.34	0.15 to 0.75	0.01
40 to 59	1.60	0.78 to 3.29	0.2	1.56	0.74 to 3.28	0.23
≥60	8.87	4.03 to 19.55	<0.01	2.77	1.11 to 6.91	0.03
all ages	0.99	0.59 to 1.65	0.96	1.01	0.63 to 1.62	0.97
Low eGFR						
all ages	0.29	0.12 to 0.69	0.01	0.62	0.24 to 1.58	0.31

[a]CI, confidence interval; eGFR, estimated GFR.
[b]Adjusted for age, gender, race/ethnicity, educational status, smoking status, diabetes, and hypertension.
[c]Estimated GFR (<60 ml/min per 1.73 m^2).

underscores the importance of studies to determine the prognostic significance of albuminuria in individuals with HCV. Although albuminuria is predictive of mortality and progression of renal disease among those with diabetes (30), its prognostic significance among those with HCV remains to be determined. However, the findings of a low prevalence of decreased eGFR and higher mean eGFR among HCV-positive participants in NHANES III do not rule out an association between HCV and progressive renal disease. This finding could occur as the result of faster progression to ESRD or death
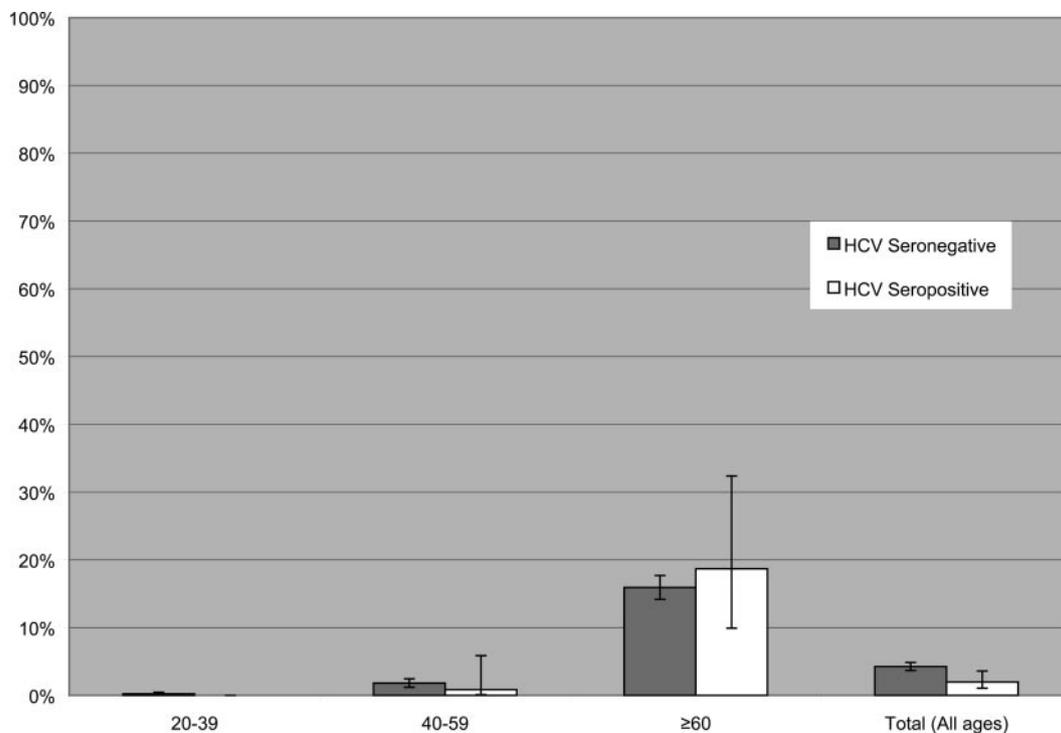
Figure 2. Prevalence of low estimated GFR (<60 ml/min per 1.73 m²) by age and hepatitis C seropositivity.

among participants with HCV. Because prevalence is determined by duration of disease state as well as incidence, a more rapid progression to renal failure or death could result in a lower prevalence of low eGFR. Other possible explanations for this finding include a lower response rate or higher competing risks (*e.g.*, from AIDS or injection drug use), leading to excess mortality among individuals with HCV and low eGFR.

Results for low GFR must be interpreted with some caution for other reasons as well. First, the small number of HCV-seropositive participants with a low eGFR resulted in wide CI for the adjusted association. Likewise, the low prevalence of abnormal eGFR did not permit us to explore this association using finer categories. Second, we did not assess GFR through direct measurement but used an estimating equation that is known to have limited accuracy, especially for individuals with cirrhosis (31,32). Because of this, we repeated the analysis excluding individuals with a platelet count $<130 \times 10^3/\mu$l, a threshold that has reasonable sensitivity for detecting cirrhosis among patients with HCV-related liver disease (20). Our results did not differ substantially, suggesting that inaccuracy in estimating GFR among participants with cirrhosis does not explain our overall findings. However, there may be differences in muscle mass as a result of wasting among patients who have HCV but do not yet have cirrhosis, which still could bias eGFR results.

There are several important limitations to our study in addition to the ones mentioned above. The major limitation is the cross-sectional design of the study, which does not allow us to make conclusions about causality. Therefore, although it is tempting to interpret the HCV–albuminuria association as evidence of a unidirectional association of HCV leading to kidney

disease, one cannot rule out the possibility that albuminuria predisposes to HCV infection. This could occur in the setting of CKD leading to exposure to HCV through blood transfusions or hemodialysis. Alternatively, CKD could cause an immuno-compromised state, increasing the risk for chronic HCV after exposure. Another limitation is that we were unable to adjust for length and type of exposure. Therefore, whereas an age-dependent association between HCV and albuminuria may suggest that development of renal disease is a time-dependent phenomena, another possibility is that there are certain uncontrolled risk factors, such as injection drug use or blood transfusion, that are more likely to occur in certain age groups and that could be causing the effect. We could not adjust for additional confounders such as injection drug use or HIV status because this information was not available in NHANES III. The extent of liver damage among individuals who were infected with HCV could not be determined because liver biopsies were not performed. Use of a second-generation enzyme immuno-assay test rather than a third-generation assay may have led to a few missed cases of HCV (33). Finally, our definition of albuminuria was based on a single measurement (sequential urinary data were not collected), which also could lead to misclassification (34).

Conclusion

This cross-sectional study demonstrates that HCV is independently associated with an increased prevalence of albumin-uria among adults who are older than 40 yr in a representative sample of the US population. In contrast, HCV did not seem to be associated with reduced eGFR in this analysis. Prospective studies are needed to determine whether chronic HCV is asso-

ciated with an increased risk for developing albuminuria and chronic renal failure.

Acknowledgments

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