Hepatitis C Is a Predictor of Poorer Renal Survival in Diabetic Patients

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OBJECTIVE — Hepatitis C virus (HCV) is highly prevalent in the U.S. and worsens renal survival in some kidney diseases. We examined the effects of HCV on renal survival in diabetic patients with renal disease.

RESEARCH DESIGN AND METHODS — HCV and diabetes status were noted in patients seen in our nephrology clinic in 2001 and 2002. Charts of diabetic patients were reviewed for demographics, blood pressure, renal function, medicines, the presence of HCV, and other factors at the initial visit and over follow-up. The effect of HCV on renal survival was determined by Cox proportional hazards, using end-stage renal disease (ESRD) as an end point.

RESULTS — Of 1,127 patients, prevalence rates for HCV were higher in African Americans than non–African Americans (8.09 vs. 3.93%, respectively, $P = 0.06$), with African-American men having the highest prevalence rates (12.7%). The charts of 312 diabetic patients were reviewed. Over 80% were African American, as were 23 of 24 patients with HCV. Compared with non-HCV patients, HCV patients were younger, had higher diastolic blood pressure, and had lower BMI. HCV patients had significantly worse cumulative renal survival by Kaplan-Meier. On Cox proportional hazards analysis, HCV was a significant predictor of reaching ESRD independent of initial renal function, proteinuria, blood pressure, sex, race, presence of diabetic nephropathy, age, or duration of diabetes (odds ratio 3.49, 95% CI 1.27–9.57, $P = 0.015$).

CONCLUSIONS — HCV is common in African Americans with diabetes and renal disease and is an independent risk factor for renal survival in this population. Prospective studies are necessary to confirm these observations.

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Hepatitis C virus (HCV) is highly prevalent in the U.S. and throughout the world (1,2), and it is known to have a wide variety of manifestations in the kidney (3,4). The renal manifestations of HCV include direct effects in the kidney, such as membranous nephropathy, cryoglobulinemia, and membranoproliferative glomerulonephritis (MPGN) (3–5). The presence of HCV worsens the progression of several renal diseases (6–8), and, like chronic renal disease (9–11), HCV is more prevalent in African Americans than in other ethnic groups. HCV has been reported to have high prevalence in diabetic patients and, more specifically, in patients with type 2 diabetic nephropathy (6,12–14). Therefore, it is possible that HCV contributes to the excess of renal disease seen in African Americans, and this effect may have a relatively greater impact among diabetic patients. In this study, we examine the effects of HCV on renal survival in a predominantly African-American cohort of patients with diabetes and renal disease.

RESEARCH DESIGN AND METHODS

— The study was approved by the Human Investigations Committee at Wayne State University School of Medicine. We identified pre–end-stage renal disease (ESRD) patients who had been seen in the nephrology clinic at Wayne State University School of Medicine over the 2-year period from 1 January 2001 to 31 December 2002. Race (by self identification and/or designation by treating nephrologist), sex, diabetes status, HCV status, and primary renal diagnosis (if available) were identified. From this group, the charts of diabetic patients were reviewed. Patients were designated as having diabetes if a history of the diagnosis was recorded in the chart or if they were on glucose-lowering medications. Patients were designated as having type 1 diabetes if they had such designation in their charts and the following clinical evidence supported this designation: age of onset <30 years, dependence on insulin from onset, history of ketoacidosis, and never off insulin for a prolonged period. All others were designated as having type 2 diabetes. Data on demographics, blood pressure, renal function, antihypertensive agents, cardiovascular disease, lipids, diabetes medication use, diabetes complications, glycemic control, and HCV virus status at the initial visit and over follow-up were extracted from clinic and hospital records. Patients who tested positive at least once for HCV antibody either before presentation or over follow-up made up the HCV group. All others were in the control group (non-HCV subjects). Given the predominance of African Americans, we grouped all patients into African-American (including all black races) or non–African American racial groups.

In general, blood pressure was mea-

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Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HCV, hepatitis C virus; MPGN, membraneoproliferative glomerulonephritis.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of diabetic patients by HCV status*

Characteristics	HCV subjects	Non-HCV subjects	*P*
*n**	24	288	—
Age (years)	55.6 ± 2.0	60.5 ± 0.78	0.078
Men/women	12 (50)/12 (50)	98 (34.0)/190 (66.0)	0.125
African American/non–African American	23 (95.8)/1 (4.2)	240 (83.3)/48 (16.7)	0.145
Duration of diabetes (years)	12.3 ± 1.9	15.3 ± 0.69	0.231
Diabetic nephropathy as primary renal diagnosis	10 (41.7)	172 (59.7)	0.090
BMI (kg/m^2)	29.9 ± 1.4	33.5 ± 0.47	0.033
Systolic blood pressure (mmHg)	157.1 ± 4.9	153.8 ± 1.6	0.560
Diastolic blood pressure	87.3 ± 2.9	81.9 ± 0.80	0.066
Estimated GFR (ml/min)	46.8 ± 7.8	42.4 ± 1.5	0.426
High urine protein	11/22 (50)	98/247 (39.7)	0.370
Number of blood pressure medications	2.67 ± 0.26	2.53 ± 0.09	0.670
On renin angiotensin system inhibitor	11/19 (57.9)	122/193 (63.2)	0.630
Cardiovascular disease	11 (45.8)	142 (50.7)	0.676
Extrarenal microvascular complications	9 (37.5)	113 (39.2)	0.99

Data are means ± SE or *n* (%). *In some cases the *n* for a variable is not equal to the total *N*.

sured by nurses or physicians using a standard mercury sphygmomanometer with the patient in the seated position. If blood pressure was checked more than once on any visit, we used the lowest documented measurement for that visit. Blood pressure over follow-up is the mean of the single lowest blood pressure taken at each follow-up nephrology clinic visit. Use of renin angiotensin system inhibitors at presentation, before presentation, or over follow-up was noted. We designated high urine protein excretion as a 24-h urine protein of >2,000 mg, a urine protein-to-creatinine ratio >2, or a value of 3+ or 4+ on a urine dipstick. We used the primary renal diagnosis as determined by the treating nephrologist. When no primary renal diagnosis was given, diabetic nephropathy was assigned if there was presence of retinopathy, micro- or macroalbuminuria, diagnosis of diabetes for at least 5 years, and absence of other obvious cause of renal disease. Extrarenal microvascular complications are defined as the documented presence of proliferative diabetic retinopathy or diabetic neuropathy.

Measurements for lipids and glycemic control were not uniformly available with respect to who had them and when they were measured. Baseline lipid, glycosylated hemoglobin, or hemoglobin A1C values are the mean of such values performed within ±6 months of the first visit. Values from >6 months after initial visit were grouped into 2-year time periods, with the first period being >6 months to 2 years. Means of values within these time periods were determined, and a weighted mean follow-up value was determined from among these means. In general, glycosylated hemoglobin (reference: 4–6.5%, determined by high-performance liquid chromatography) was the primary measurement performed in our clinical laboratory, with the hemoglobin A1C calculated from that value. Therefore, glycosylated hemoglobin was used in analysis.

We used the Modification of Diet in Renal Disease (MDRD) equation to estimate glomerular filtration rate (GFR) (15). Patients were classified according to chronic kidney disease (CKD) stage per the criteria of the National Kidney Foundation (16). Briefly, this classification includes five stages of kidney disease based on GFR, with stage 1 being GFR >90 ml/min with albuminuria and stage 5 being GFR <15 ml/min or ESRD. Initiation of renal replacement therapy (ESRD) was the primary end point, but doubling of creatinine, change in CKD stage, and cardiovascular events were also noted. Cardiovascular outcomes included coronary artery disease (unstable angina, myocardial infarction, and asymptomatic occlusive coronary disease), congestive heart failure, and stroke (including transient ischemic attack).

Statistical analysis

Data were entered into StatView (SAS, Cary, NC) and analyzed. In the analysis for effects on renal survival, we excluded patients with no follow-up visits and those who presented with stage 5 CKD. Kaplan-Meier analysis was used to determine the effect of HCV on renal survival, using ESRD as an end point. Cox proportional hazards was used to determine the effect of HCV and other individual variables on renal survival, with results expressed as hazard ratio and 95% CI. In the multivariate model, HCV was the initial variable entered, with subsequent variables entered in stepwise fashion in order of decreasing strength of correlation to ESRD as determined by the *P* value from univariate analysis (Table 2). Data had to be available in at least half of the cohort to be entered into the multivariate analysis. In renal survival analysis, data on those not reaching ESRD was censored at the time of the last clinic visit (duration of follow-up). The relationship of HCV to cardiovascular events (prevalent and incident) was by logistic regression. Comparison between continuous variables was by unpaired *t* test and between descriptive variables was by χ^2. *P* values <0.05 were considered statistically significant.

RESULTS — We identified 1,127 unique pre-ESRD patients who were seen in the 2-year period. Eighty (7.1%) had HCV and 395 (35.1%) had diabetes. Race was determined on 1,063 patients, of which 83.1% were African American. There was no significant correlation between prevalence of HCV and diabetes in any race or sex group. Diabetes was more common among women (38.8 vs. 29.9% in men, $P = 0.002$) and tended to be more

Table 2—*Cox proportional hazards analysis for predictors of ESRD in diabetic subjects seen in an urban academic nephrology clinic*

Characteristic		*P*
Univariate analysis		
HCV positive	3.69 (1.83–7.45)	0.0003
Other significant factors		
Sex (men)	1.84 (1.08–3.13)	0.026
African-American race	3.22 (1.00–10.3)	0.049
Diabetic nephropathy	2.23 (1.19–4.17)	0.012
Initial mean arterial blood pressure	1.02 (0.998–1.03)	0.081
Estimated GFR	0.947 (0.926–0.968)	<0.0001
Urine protein (high)	3.72 (1.96–7.07)	<0.0001
Number of blood pressure medications on presentation	1.27 (1.08–1.51)	0.0053
Systolic blood pressure on follow-up	1.03 (1.02–1.05)	<0.0001
Diastolic blood pressure on follow-up	1.06 (1.03–1.10)	0.0002
Baseline total cholesterol (n = 115; 15 events)	0.979 (0.966–0.992)	0.0012
Multivariate model		
HCV positive*	3.38 (1.39–8.21)	0.007
HCV positive†	3.49 (1.27–9.57)	0.015

Data are odds ratio (95% CI). *Model includes initial renal function, urine protein excretion, blood pressure, sex, race, and presence of diabetic nephropathy. In addition to HCV status, these factors remain significant on multivariate analysis (diastolic blood pressure on follow-up was the only blood pressure variable remaining significant). †Includes variable as above plus age, duration of diabetes, and renin angiotensin system inhibitor status at presentation. Age, initial renal function, and urine protein excretion remained significant in addition to HCV status.

common among African Americans. HCV tended to be more prevalent in African Americans (8.1 vs. 4.1% non–African Americans, $P = 0.06$), with African-American men having the highest prevalence (12.7 vs. 5.1% in African-American women, $P = 0.0001$).

A total of 387 charts were available for review from the diabetic patients. Twenty-six patients with HCV were identified, and of these 25 were African American. Two patients (both with CKD stage 5) in the HCV group and 73 patients (35 with CKD stage 5 and 38 with no follow-up) in the non-HCV group were excluded from further analysis. Baseline characteristics for the 24 HCV and 288 non-HCV patients included in this analysis are shown in Table 1. Twenty-two non-HCV subjects had type 1 diabetes, but all HCV-positive patients had type 2 diabetes. At presentation, HCV patients had significantly lower BMI. HCV patients tended to be younger, to have higher diastolic blood pressure, and to be less likely to have diabetic nephropathy as their primary renal diagnosis than non-HCV patients. There were no significant differences in other variables. HCV genotype was available in only 11 patients. Eight (72.7%) patients had genotype 1, and 3 patients had genotype 2. The most common primary renal diagnoses after diabetic nephropathy were hypertensive nephrosclerosis (~30% in non-HCV and 20% in HCV subjects) glomerular diseases (~3% in non-HCV subjects).

Compared with non-HCV, HCV patients had significantly poorer renal survival. A total of 54 patients reached ESRD (10 HCV [41.7%] and 44 non-HCV [15.3%] subjects, $\chi^2 = 0.0030$). Kaplan-Meier analysis revealed cumulative renal survival to be significantly worse in HCV patients (Fig. 1, $P < 0.0001$, log rank [Mantel-Cox]). The rate of loss of estimated GFR was -24.8 ± 10.4 and -2.14 ± 2.32 ml · min^{-1} · year^{-1} ($P = 0.008$) in HCV and non-HCV subjects, respectively. On univariate Cox proportional hazards analysis, HCV patients had over threefold risk for ESRD over the period of follow-up than non-HCV patients (Table 2). Other factors found to be significant predictors of reaching ESRD are also shown in Table 2. These include African-American race, male sex, diabetic nephropathy as the primary renal diagnosis, urine protein excretion, and initial renal function (using either estimated GFR or serum creatinine). HCV-positive status remained a predictor for reaching ESRD, with inclusion of many of these factors in the model indicating that it is an independent predictor of renal survival in diabetic subjects. Ninety patients reached the combined end point of ESRD or doubling of serum creatinine. After adjustment for factors in model 1, HCV-positive patients were 2.68 times more likely to reach the

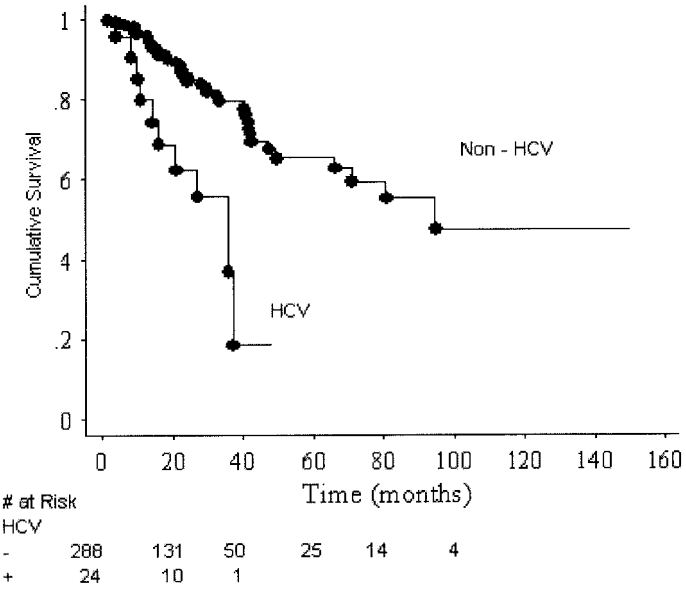

Figure 1—*Kaplan-Meier curve for renal survival using ESRD as an end point in HCV and non-HCV patients with diabetes* ($P < 0.0001$).

Table 3—*Follow-up characteristics of HCV and non-HCV patients*

Characteristic	HCV subjects	Non-HCV subjects	*P*
n	24	288	—
Diastolic blood pressure on follow-up (mmHg)	84.7 ± 2.3	79.6 ± 0.58	0.0154
Weighted mean follow-up LDL (mg/dl)	89.6 ± 14.1 (*n* = 9)	124.2 ± 3.54 (*n* = 148)	0.0201
Weighted mean follow-up total cholesterol (mg/dl)	166.8 ± 15.6 (*n* = 11)	210.8 ± 4.23 (*n* = 170)	0.0108
Weighted mean glycosylated hemoglobin (%)	9.43 ± 1.1 (*n* = 10)	9.94 ± 0.28 (*n* = 139)	0.646
Renin angiotensin system inhibitor (ever)	19/23 (82.6)	242/270 (89.6)	0.295
Mean number of blood pressure medications over follow-up	3.11 ± 0.25	3.09 ± 0.09	0.959
Follow-up time (months)	19.5 ± 2.6	25.2 ± 1.5	0.269

Data are means ± SE or *n* (%).

combined end point (95% CI 1.36–5.27) ($P < 0.0043$) than non-HCV patients.

HCV patients had significantly higher diastolic blood pressure over follow-up (Table 3). HCV patients also had lower LDL and total cholesterol, but glycemic control was not different. There was no difference between HCV-positive and non-HCV subjects for incident cardiovascular events or the likelihood of having extrarenal microvascular complications.

CONCLUSIONS — In a cohort that was >80% African American, we found that diabetic patients with HCV had worse renal survival, and these effects of HCV were independent of other factors shown to affect renal survival. In support of our observation, a similar effect of HCV was observed in a retrospective study of patients with CKD who underwent renal biopsy in northeastern Japan (6). In that study, the prevalence rate of HCV was 4.1% in the >2,300 patients who had a renal biopsy. However, the prevalence of HCV was highest (19.5% [24 of 123]) in patients with type 2 diabetes who had a renal biopsy. Of interest, renal biopsies were done in patients with diabetes because the history was inconsistent with diabetic nephropathy (hematuria, heavy proteinuria in absence of retinopathy, or short history of diabetes). Likewise, we found that diabetic patients with HCV were less likely to have diabetic nephropathy as their primary diagnosis. Unlike our study, the Japanese study did not show a significant difference in progression to ESRD between HCV and non-HCV diabetic patients. However, similar to our findings, the rate of progression of renal disease was worse in the HCV group (6).

We can only speculate as to why diabetic patients with HCV have worse renal survival. In our study, renal function was poor at presentation in both groups, with the majority of patients presenting with stage 3 or higher CKD. Therefore, the entire cohort was at significant risk of renal disease progression. HCV patients differed from non-HCV patients in only a few areas. Among these differences, blood pressure would be most likely to affect renal survival. However, the effects of HCV on renal survival were independent of both initial and follow-up blood pressure. It is interesting that LDL and total cholesterol were significantly lower in the HCV group over the course of follow-up. It is not clear why this is the case, but it may represent an increased state of inflammation or altered caloric metabolism. Notably, ESRD patients with lower total cholesterol, homocysteine, and serum creatinine have worse survival (17,18). Similarly, lower BMI is also associated with poorer overall survival among ESRD patients (19). It is hypothesized that these parameters represent increased inflammation in ESRD patients. We are not able to comment on other inflammatory parameters in our cohort, as they were not consistently checked. However, we have observed in a separate work that an elevated anti-nuclear antibody predicts worse renal survival in a cohort of diabetic and nondiabetic HCV patients (20). Whether this serologic test indicates increased autoimmunity, which is sometimes seen with HCV (21), or is a marker for increased inflammation or both is not clear at this time.

Poorer renal survival in the HCV group may be due to direct effects of HCV in the kidney. However, we are unable to say if worse renal survival was due specifically to HCV-related glomerular disease due to limited data. This is not likely to be the explanation, as HCV-related glomerular diseases such as MPGN are thought to be relatively uncommon. For example, in one study, only 4 of 91 HCV-positive liver transplant recipients had biopsy-proven MPGN (22). In the Japanese studies mentioned above, 3 of 24 type 2 diabetic patients with HCV who had renal biopsy had evidence of MPGN (6).

An association between HCV and type 2 diabetes has been reported by several groups (6,12–14,23,24). The higher prevalence of HCV in African Americans parallels the higher prevalence and incidence rates of type 2 diabetes seen in this group (23). Unlike the Japanese study, we did not see any correlation between HCV positivity and the presence of type 2 diabetes. One possible reason why HCV was not associated with higher prevalence of type 2 diabetes is that HCV prevalence was highest in African-American men, a group at relatively lower risk for type 2 diabetes when compared with African-American subjects (25,26).

While this analysis is limited, in that it is retrospective and has a relatively small number of HCV patients, it remains an important and novel observation. Because all patients did not have HCV serology done, it is conceivable that some HCV-positive patients were missed. However, all patients had HCV status checked upon entering the ESRD program, so HCV status is known among those reaching the end point. In addition, a single antibody test for HCV may be a false-positive, but we have corroborating evidence (subsequent HCV antibody, viral load, or genotype) in >80% of the cases. Unfortunately, we do not have sufficient data to comment on the state of liver disease in HCV patients.

In summary, we have observed HCV to be a predictor of progression to ESRD in a cohort of predominantly African-

American patients with diabetes and renal disease. As both type 2 diabetes and HCV are more common among African Americans and as type 2 diabetes is the number one cause of ESRD in African Americans, it is important to determine the mechanisms by which HCV may worsen renal survival in this group. Physicians who confirm the presence of HCV in patients with diabetes, especially African Americans, should be aware of their increased risk for progression to ESRD and should pay close attention to other modifiable risk factors, such as blood pressure control. It is important that prospective studies be performed to confirm these preliminary observations.

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