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End-stage Renal Disease and African-American Race are Independent Predictors of Mild Liver Fibrosis in Patients with Chronic Hepatitis C Infection

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Abstract

Recipients of hemodialysis for end-stage renal disease have a higher prevalence of hepatitis C virus (HCV) infection relative to the general U.S. population. However, the natural course of HCV infection in patients with renal failure, including African-Americans and Caucasian-Americans, is not well known. We compared the degree of liver inflammation and fibrosis in patients with HCV infection, with and without end-stage renal disease. This was a cross-sectional study of 156 HCV patients with end stage renal disease (130 African Americans and 26 Caucasian Americans) with a liver biopsy between 1992 and 2005. The control group consisted of 138 patients (50 African Americans) with HCV infections and a serum creatinine less than 1.5 mg/dL with a liver biopsy between 1995 and 1998. Specimens were graded for inflammation and fibrosis using Knodell Histological Activity Index. Compared to patients without renal impairment, HCV patients with renal failure were older and more likely to be African American. Patients with renal impairment had lower mean serum transaminases, a higher mean serum alkaline phosphatase levels (all $p < 0.0001$) and less hepatic necro-inflammation (Knodell Inflammation score -I, II and III; $p < 0.05$) and fibrosis (Knodell fibrosis > 4 ; $p < 0.0001$). There were no racial differences in serum liver chemistry and histology scores among patients with renal failure. In a multivariate analysis, younger age, end stage renal disease, African American race, and a lower serum alkaline phosphatase were associated with lower odds for advanced liver fibrosis. Thus HCV patients with end stage renal disease had a lower degree of hepatic inflammation and fibrosis compared to those without renal disease, independent of race.

Keywords

End-stage renal disease; Hepatitis C; Liver fibrosis; Cirrhosis

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Introduction

Chronic hepatitis C infection is the most common cause of chronic liver disease and cirrhosis in the United States and a major risk factor for hepatocellular carcinoma [1]. Approximately 2.7 million Americans are infected with HCV [1]. The prevalence of HCV infections varies by many factors including race, with a higher prevalence in African Americans (AA) compared to Caucasian-Americans (CA) [1]. HCV infection is also more common in patients with end-stage renal disease (ESRD) on chronic hemodialysis. In the United States, the prevalence of HCV infection is estimated to be up to 10% among hemodialysis patients [2]. A prospective, observational study of adult hemodialysis patients from 308 dialysis facilities in Europe, Japan, and the United States found a mean HCV prevalence of 13.5%, with a range from 2.6% to 22.9% [3]. It is well known that chronic HCV infection adversely affects survival in patients with ESRD [4, 5]. In a U.S. multicenter case-control study, with a median follow-up of 7 years, death due to liver disease occurred in 14% of HCV antibody-positive subjects and only 2% of HCV antibody-negative controls [4]. In multivariate analysis, the relative risk (RR) for death from all causes in anti-HCV-positive patients with ESRD was 1.41 (95% CI, 1.01–1.97), and the RR of death from liver disease or infection was 2.39 (95% CI, 1.28–4.48). Similar results were reported in another multicenter prospective study from Japan [5]. Paradoxically, several cross-sectional studies have reported significantly lower serum alanine aminotransaminase (ALT) concentrations, and less hepatic necro-inflammation and fibrosis in HCV patients with ESRD compared to those without ESRD [6–8]. Some of the studies were limited by a small sample size, and the association of factors such as race, sex, age, alcohol intake, and comorbid conditions with the degree of liver inflammation and fibrosis was often not examined. Both ESRD and HCV infection are more common in AA compared to CA [9, 10]. Medicare claims files data from 1997 through 2000 revealed a 3.5 times greater odds of having ESRD in AA compared to CA [9]. The prevalence of HCV infection in AA is twice that in CA (3.5 vs. 1.5%) [10]. On the other hand, several studies have observed milder liver necro-inflammation and less fibrosis in AA compared to CA patients with HCV and no renal disease [11–13]. The extent to which the higher prevalence of AA race in ESRD contributes to the lower necro-inflammation and hepatic fibrosis in HCV patients with ESRD is not clear. The aims of the current study were: 1) to compare the degree of liver inflammation and fibrosis in a large cohort of HCV-infected patients with and without ESRD; and 2) to identify the association of liver necro-inflammation and fibrosis with race and ESRD in patients with chronic HCV infections.

Material and Methods

Study Design

This was a retrospective study of 156 HCV-positive patients with ESRD who were evaluated for kidney transplantation at the University of Maryland Medical Center between January 1992 and January 2005. All patients underwent liver biopsy as part of pre-transplant evaluation for patients with chronic HCV infection. The controls were HCV-infected patients with no kidney disease (serum creatinine less than 1.5 mg/dL), a subset of patients with chronic HCV, evaluated at the University of Maryland Medical Center Hepatology Clinic for chronic HCV infection between 1995 and 1998, previously reported by Crosse et al [11]. Sixty-two patients in Crosse's study sample who had a missing baseline serum creatinine and 23 with a serum creatinine >1.5 mg/dl were excluded. HCV infection was confirmed in both ESRD and control patients by serum HCV RNA tests. Each patient had at least one liver biopsy available for review. Liver biopsy specimens were fixed in neutral-buffered formalin and routinely stained with Hematoxylin and Eosin and Masson's trichrome. Patients with HIV/HCV or HBV/HCV co-infections, and prior organ transplantation recipients were excluded. The study was approved by the Institutional

Review Board for Human Subject Research at the University of Maryland Baltimore in January 2005.

Data Collection

Data regarding patient's age, sex and race, as well as a history of alcohol, intravenous drug use, and blood transfusion were collected. Alcohol abuse was defined as ingestion of more than 2 alcoholic beverages daily. Serum alanine aminotransaminase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, and albumin levels were collected at the time of the initial office visit. All liver biopsy slides were reviewed by the same pathologist using Knodell Histological Activity Index (HAI) criteria [14]; a semi-quantitative and reproducible histological scoring system of liver biopsy that consists of four categories, graded semi-quantitatively; HAI-I: periportal hepatocyte-bridging necrosis (0–10), HAI-II: intralobular degeneration (0–4), HAI-III: portal inflammation (0–4), and HAI IV: fibrosis (0–4)]. The total HAI score (range 0–22) is the sum of the four components.

Statistical analysis

Continuous variables were expressed as means $\pm$ standard deviation or medians $\pm$ interquartile range (IQR) depending on the distribution, and were analyzed using Student's t-tests or Wilcoxon-Mann-Whitney tests, respectively. To identify factors associated with liver inflammation and fibrosis, multivariable analysis was performed separately for each HAI category (I–IV). In these analyses, HAI categories were dichotomized into 'mild' and 'moderate to severe'. An HAI-I score >5 and HAI-II, HAI-III, and HAI-IV scores of >3 were defined as 'moderate to severe'. The independent variables were age, sex, race, renal function status, AST, ALT, alkaline phosphatase, albumin, total bilirubin, history of alcohol abuse and IV drug use. All statistical analyses were performed using SAS[®] 9.1 computer statistical software (SAS Institute Inc., Cary, NC).

Results

Patient Demographics

As summarized in Table 1, HCV patients with ESRD were older ($p<0.0001$), and predominantly AA ($p<0.0001$) and male ($p=0.006$). Patients with ESRD were also more likely to have blood transfusion as a risk factor for HCV transmission ($p<0.0001$). The prevalence of intravenous (IV) drug use was similar in both groups, but alcohol abuse was more common in HCV patients with ESRD. Seventy-five percent of patients in ESRD group were on hemodialysis and 8% on peritoneal dialysis. Seventeen percent of patients with ESRD were not on dialysis at the time of evaluation for kidney transplantation and liver biopsy.

Liver Chemistry

Compared to HCV patients with no renal disease (Table 1), HCV patients with ESRD had a higher mean serum alkaline phosphatase level and lower mean serum ALT, AST, total bilirubin and albumin levels (all $p<0.0001$). Sixty-nine percent of patients with ESRD and only 12% of patients without renal disease had ALT levels lower than 40 IU/L. Among patients with ESRD, there were no racial differences in serum ALT, AST, total bilirubin, alkaline phosphatase and albumin. In contrast, among patients without renal disease, AA had lower mean ALT (96.3 vs. 126.9 IU/L, $p=0.04$) and albumin (3.8 vs. 4.1 g/dL, $p=0.03$) levels; there were no racial differences in serum AST, alkaline phosphatase and total bilirubin levels.

Hepatic Histology

HCV patients with ESRD had a lower median total HAI score than patients with no renal disease (Figure 1-A). This included less periportal hepatocyte-bridging necrosis (HAI-I), intralobular degeneration (HAI-II), portal inflammation (HAI-III), and liver fibrosis (HAI-IV) (Figure 1-B). Within AA and CA, lower total and individual HAI component scores were also observed in patients with ESRD (Table 2). There were no racial differences in total and individual HAI scores in patients with ESRD. Moderate to severe portal inflammation and liver fibrosis lesions were also more frequent in patients with no ESRD ($p < 0.0001$) (Table 3). However, there were no racial differences in the frequency of moderate to severe liver necro-inflammation and fibrosis in patients with or without renal disease (data not shown).

Regression Analysis

In multivariable logistic analysis for the total study population (Table 4 col. 2), ESRD, AA race, age < 50 years and serum alkaline phosphatase level less than 120 IU/L were independently associated with a lower odds ratio for advanced liver fibrosis (HAI-IV > 3) after adjusting for sex, AST, ALT, albumin, total bilirubin levels, alcohol, and IV drug use. Among patients with ESRD (Table 4, col. 3), the odds ratio for advanced liver fibrosis (HAI-IV > 3) was lower those with a serum alkaline phosphatase less than 120 IU/L. AA race was not associated with a lower odds for advanced fibrosis in patients with ESRD, though statistical significance ($p = 0.05$) was marginal. In patients without renal disease (Table 4, col. 4), AA race, higher albumin and lower alkaline phosphatase levels were associated with lower odds for advanced liver fibrosis.

Discussion

Patients with chronic HCV infection and ESRD had significantly lower serum aminotransferase and less hepatic necrosis, inflammation and fibrosis than control patients with HCV and no renal disease. There were no racial differences in serum liver tests and liver histology among HCV patients with ESRD. AA race, age < 50 years, ESRD and a serum alkaline phosphatase level < 120 IU/L were independently associated with lower odds of advanced liver fibrosis and cirrhosis (HAI-IV score > 3) in multivariable regression analysis.

Prior studies have found significantly lower serum ALT and AST and less severe hepatic inflammation and fibrosis in patients with HCV and ESRD [6–8, 15, 16]. However, most of these studies were limited by small sample sizes and lack of control for other risk factors for liver fibrosis. We studied the association between ESRD and liver necro-inflammation, fibrosis and overall histological activity in a large, racially diverse cohort. Thus, the study provided a unique opportunity to examine the potential confounding effects of race and ESRD on HCV-related liver disease expression.

In keeping with previous studies, we observed lower serum AST, ALT, albumin, total bilirubin and less necro-inflammation and fibrosis in ESRD patients with HCV compared to control patients with HCV and no renal disease. In addition, both severe portal inflammation (HAI-III > 3) and liver fibrosis (HAI-IV > 3) were less prevalent among patients with ESRD. Among patients with ESRD, HAI scores did not differ between AA and CA. In contrast, among patients without ESRD, AA race was independently associated with less liver fibrosis.

Variables associated with more advanced liver fibrosis in HCV patients without renal disease have been extensively characterized in previous studies, and include Caucasian race, older age at the time of infection, longer duration of HCV infection, obesity, hepatic

steatosis, and alcohol abuse [17–20]. However, the variables associated with advanced liver fibrosis in patients with HCV and ESRD are not well understood. Any degree of hepatic steatosis and a platelet count less than $130 \times 10^9/L$ were associated with advanced liver fibrosis (HAI-IV > 3) in a study by Hu et al [8]. In the present study, AA race, ESRD, age <50 years, and lower serum alkaline phosphatase level were independently associated with lower odds for moderate to severe liver fibrosis (bridging fibrosis or cirrhosis).

It is well established that AA with chronic HCV infection and no renal disease have milder liver necro- inflammation and fibrosis than CA patients with similar durations of HCV infection [11]. These racial differences in liver histology are not explained by a variance in hepatic iron content [11]. It has been postulated that a less vigorous HCV-specific CD4 T-cell response in AA, and racial differences in HLA haplotypes may explain the lower degree of liver injury and disease severity in AA patients [21]. AA race was also associated with lower odds for advanced fibrosis in patients without renal disease, but not in patients with ESRD. These observations indicate that lower liver fibrosis level in patients with ESRD was not explained by the higher proportion of AA in this subgroup. However, it is possible that an association between race and liver fibrosis could be obscured by the smaller number of CA patients with ESRD.

A serum alkaline phosphatase <120 IU/L was associated with lower odds for advanced liver fibrosis in patients with and without ESRD in the current study. A lower serum alkaline phosphatase was one of several variables associated with less advanced (Ishak stage 0–2) liver fibrosis in a report by Fontana [22], though the biological basis has not been defined. Several prior studies have found an association between alcohol abuse and more advanced liver fibrosis and higher mortality rates in patients with chronic HCV [17]. In contrast, alcohol abuse, defined as >2 alcoholic beverages per day was not an independent predictor of more advanced liver fibrosis in the current study. These results should be interpreted with caution, as they are based on patient recall and we were not able to quantify alcohol intake and exposure above the 2 beverage threshold.

The pathophysiologic basis for differential expression of liver necro-inflammation and fibrosis in HCV patients with and without ESRD is poorly understood. One study suggested that the increase in hepatocyte growth factor levels in HCV-infected patients with ESRD protects liver cells against HCV-induced apoptosis and stimulates hepatocyte proliferation [23]. HCV infection among hemodialysis patients was proposed to be associated with decreased plasma oxidative load [24]. Another study assessed the histopathological features of hepatitis C in renal transplant candidates, comparing changes among hemodialysis patients compared to those with predialysis chronic renal disease [25]. Patients on hemodialysis exhibited less necro-inflammation and fibrosis. This finding may suggest a role for hemodialysis in delaying liver fibrosis associated with HCV infection in patients undergoing hemodialysis.

This study has several limitations. Because of the retrospective design, data on duration of HCV infection, chronic renal disease and ESRD, duration of dialysis, etiology of renal disease, HCV genotype and viral load, and prior HCV treatment were not collected. Age has been viewed as a surrogate marker for duration of HCV infection in patients without ESRD, but is not a reliable indicator of length of infection in ESRD patients who often have nosocomial transmission during hemodialysis. ESRD patients in this study represent those were referred to examine their eligibility for renal transplantation, but not renal and liver transplantation. This excludes ESRD patients with more advanced fibrosis or cirrhosis. On the other hand, patients on the liver transplantation waiting list were also excluded from the control group to avoid referral bias.

In conclusion, our study demonstrated that HCV patients with ESRD exhibit less hepatic necro-inflammation and fibrosis than those without renal disease. Milder hepatic necro-inflammation and fibrosis in patients with ESRD is not explained by the higher prevalence of renal disease in AA.

Abbreviations

AA	African-American
CA	Caucasian-American
ESRD	end-stage renal disease
HIA	histological activity index
OR	odds ratio
RR	relative risk
CI	confidence interval
ALT	alanine aminotransferase
AST	aspartate aminotransferase
IQR	interquartile range
HCV	hepatitis C virus

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Figure 1. Comparison of HAI scores in chronic HCV patients with and without renal disease: (A) Total HAI score; (B) HAI I-IV scores

Results expressed as median and inter-quartile range (IQR) and compared using Wilcoxon-Mann-Whitney test. HAI: histological activity index; ESRD: end-stage renal disease; no RD: no renal disease.

Table 1

Demographics and clinical features of patient populations

Variables ^a	ESRD (n=156)	No renal disease (n=138)	p
Age, years	54.0 (9.9)	44.8 (8.1)	0.0001
Male (%)	76.9	62.3	0.0064
AA (%)	83	36	0.0001
Alcohol abuse (%)	46.1	23.9	0.0001
IV drug use (%)	39.1	35.0	0.4726
Blood transfusion (%)	39.7	18.8	0.0001
Albumin (g/dL)	3.5 (0.7)	4.0 (0.5)	0.0001
ALT (IU/L)	40.3 (30.1)	115.8 (96.5)	0.0001
AST (IU/L)	37.5 (25.1)	885.9 (62.5)	0.0001
Total bilirubin (mg/dL)	0.65 (0.47)	0.99 (0.92)	0.0001
Alkaline phosphatase (IU/L)	136.5 (97.7)	92.2 (42.4)	0.0001

^aContinuous variables expressed as mean (SD); ESRD: end-stage renal disease; AA: African-American; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table 2
Lower HAI Scores in African-Americans and Caucasian-Americans with ESRD

	African-American (n = 182)		Caucasian-American (n = 112)	
	ESRD (n=132)	No renal disease (n=50)	ESRD (n=24)	No renal disease (n=88)
HAI				
I	1.0 (1.0–1.0)	3.0 (1.0–3.0)	1.0 (1.0–3.0)	3.0 (1.0–3.0)
II	1.0 (0.0–2.0)	1.0 (1.0–2.5)	1.0 (0.5–1.5)	1.0 (1.0–3.0)
III	1.0 (1.0–3.0)	3.0 (2.5–3.0)	3.0 (1.0–3.0)	3.0 (2.5–3.0)
IV	1.0 (0.0–1.5)	2.0 (1.0–3.0)	1.0 (0.0–1.0)	1.0 (1.0–3.0)
Total	5.0 (3.0–6.5)	8.0 (7.0–11.0)	6.0 (3.0–9.0)	8.0 (6.0–10.0)
				p
				0.0825
				0.1011
				0.0083
				0.0027
				0.0020

Results expressed as median (IQR); results compared using non-parametric Mann-Whitney test; ESRD: end-stage renal disease, HAI: histological activity index.

Table 3

Less frequent moderate to severe HAI in patients with ESRD

HAI scores	ESRD (n=156) n (%)	No renal disease (n=132) n (%)	p
HAI-I $\geq$ 5	2 (1.3)	5 (3.6)	0.25
HAI-II $\geq$ 3	37 (23.7)	38 (27.5)	0.50
HAI-III $\geq$ 3	88 (56.4)	104 (75.4)	<0.0001
HAI-IV $\geq$ 3	20 (12.8)	58 (42.0)	<0.0001

Results compared with using Fisher's exact tests; ESRD: end-stage renal disease; HAI: histological activity index.

Table 4Variables associated with advanced liver fibrosis (HAL-IV ≥ 3)

Variable	Study population				ESRD				No renal disease			
	OR	95% CI	p		OR	95% CI	p		OR	95% CI	p	
ESRD (ref. no renal disease)	0.07	0.01–0.29	0.003		-	-	-		-	-	-	
African-American race (ref. CA race)	0.26	0.09–0.74	0.01		0.26	0.06–1.00	0.05		0.37	0.15–0.78	0.02	
Age < 50 years (ref. ≥ 50 years)	0.17	0.05–0.65	0.01		1.04	0.98–1.11	0.17		1.05	0.99–1.12	0.11	
Female sex (ref. Male)	2.00	0.76–5.26	0.16		1.13	0.34–3.74	0.83		0.98	0.44–2.20	0.97	
ALT < 40 IU/L (ref. ≥ 40 IU/L)	0.51	0.14–1.88	0.31		0.98	0.29–3.35	0.89		0.34	0.08–1.52	0.16	
AST < 40 IU/L (ref. ≥ 40 IU/L)	0.58	0.19–1.78	0.34		0.71	0.21–2.39	0.58		0.71	0.21–2.39	0.58	
Albumin > 3.5 g/dL (ref. ≤ 3.5 g/dL)	1.40	0.49–4.04	0.53		0.97	0.35–2.73	0.96		0.23	0.06–0.79	0.02	
Total bilirubin < 1.2 mg/dL (ref. ≥ 1.2 mg/dL)	0.83	0.22–3.11	0.77		0.63	0.16–2.50	0.51		0.64	0.26–1.53	0.31	
Alkaline phosphatase < 120 IU/L (ref. ≥ 120 IU/L)	0.21	0.07–0.29	0.004		0.26	0.08–0.84	0.02		0.27	0.08–0.83	0.02	
History of alcohol abuse (ref. no alcohol abuse)	0.63	0.24–1.67	0.35		1.03	0.34–3.15	0.96		1.50	0.61–3.79	0.37	
History of IVUDU (ref. no IVUDU)	1.02	0.39–2.70	0.96		1.19	0.37–3.87	0.77		0.88	0.38–2.01	0.76	

HAL: histological activity index; ESRD: end-stage renal disease; CA: Caucasian-American; OR: odds ratio; CI: confidence interval; ALT: alanine aminotransferase; AST: aspartate aminotransferase; IVUDU: intravenous drug use.