Impact of Diabetes and Hepatitis after Kidney Transplantation on Patients Who Are Affected by Hepatitis C Virus

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Abstract. Complications associated with use of donor hepatitis C–positive kidneys (DHCV+) have been attributed primarily to posttransplantation liver disease (as a result of hepatitis C disease). The role of posttransplantation diabetes has not been explored in this setting. With the use of the United States Renal Data System database, 28,942 Medicare KT recipients were studied from January 1, 1996, through July 31, 2000. Cox proportional hazards regression models were used to calculate adjusted hazard ratios (AHR) for the association of sero-pairs for HCV (D+/R−, D+/R+, D−/R+ and D−/R−) with Medicare claims for *de novo* posttransplantation HCV and posttransplantation diabetes. The peak risk for posttransplantation HCV was in the first 6 mo after transplantation. The incidence of posttransplantation HCV after transplantation was 9.1% in D+/R−, 6.3% in D+/R+, 2.4% in D−/R+, and 0.2% in D−/R−. The incidence of posttransplantation diabetes after transplantation also peaked early and was 43.8% in D+/R−, 46.6% in D+/R+, 32.3% in D−/R+, and 25.4% in D−/R−. Associations for both complications were significant in adjusted analysis (Cox regression). Both posttransplantation HCV (AHR, 3.36; 95% confidence interval, 2.44 to 4.61) and posttransplantation diabetes (AHR, 1.81; 95% confidence interval, 1.54 to 2.11) were independently associated with an increased risk of death, but posttransplantation diabetes accounted for more years of life lost, particularly among recipients of DHCV+ kidneys. Posttransplantation diabetes may contribute substantially to the increased risk of death associated with use of DHCV+ kidneys and accounts for more years of life lost than posttransplantation HCV. Because HCV infection acquired after transplantation is so difficult to treat, methods that have been shown to reduce viral transmission warrant renewed attention.

Hepatitis C virus (HCV) infection, whether present in donors or recipients, has been associated with increased risk of mortality after kidney transplantation (1–5). Previous studies of the impact of using donor HCV antibody–positive kidneys (DHCV+) in transplantation have focused on the development of posttransplantation liver disease (6,7) and concluded that posttransplantation liver disease was not a major contributor to morbidity and mortality in this setting. Although liver disease was a more frequent cause of death among recipients of DHCV+ kidneys, it was not the leading cause of death in this circumstance (1,2). Therefore, liver disease alone does not explain the higher risk of death associated with use of DHCV+ kidneys. Nevertheless, mortality increases stepwise in association with donor-recipient HCV sero-pairing (1), similar to the findings of sero-pairings for cytomegalovirus (CMV) (8–11). If use of DHCV+ kidneys truly contributes to a higher risk of death after kidney transplantation, then we would expect to see an association between DHCV+ kidneys and a nonfatal complication that could be a link in the causal chain for mortality. Such a complication would need to occur early and affect a large number of recipients of DHCV+ kidneys.

Posttransplantation diabetes is a plausible candidate for such a link. Recipient HCV infection has already been reported as a risk factor for posttransplantation diabetes (12–14). Posttransplant diabetes is also associated with increased mortality after kidney transplantation, occurring earlier after the onset of diabetes than in the general population (13,14).

Neither the association of donor/recipient HCV antibody status with the risk of HCV and posttransplantation diabetes occurring after kidney transplantation nor the relative contribution of each complication to mortality by donor/recipient HCV antibody status has been described previously in a large population. Therefore, we performed a retrospective cohort study of the U.S. kidney transplant population. Our objective

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was to determine the relative degree of risk for posttransplantation HCV and posttransplantation diabetes for various seroparings for HCV, similar to methods previously performed for CMV, adjusted for other factors. We hypothesized that posttransplantation diabetes would be significantly associated with donor and recipient HCV status, would occur early after kidney transplantation, and would be more common than posttransplantation hepatitis. We also hypothesized that posttransplantation diabetes would contribute more to observed mortality after kidney transplantation by donor and recipient HCV status than posttransplantation hepatitis.

Materials and Methods

Patients and Sources

All data were drawn from the United States Renal Data System (USRDS). The USRDS contains clinical records from various sources and administrative records from Medicare covering all of ESRD, including kidney transplant, in the United States. Details of the files used for data abstraction for this study, as well as limitations of Medicare claim data, have been described previously (15) and differ by year of selection and limitations of key variables, notably the use of the Centers for Medicare/Medicaid Studies Medical Evidence Form (CMS 2728) (16). Files were merged using unique identifiers. The most recent files released by the USRDS include follow-up (including dates of death) until October 31, 2001. However, the most recent dates for Medicare claims available are December 31, 2000. The present study limited analysis to the first kidney transplant that occurred in an individual recipient with documentation of Medicare as primary payer during the period from January 1, 1996, to July 31, 2000 (which could include a repeat transplant or multiple-organ transplant). Assessment of *de novo* diabetes excluded patients with a known history of diabetes or Medicare claims for diabetes before the date of kidney transplantation, as per previous reports (13,14).

Outcomes

Our primary outcomes were Medicare claims for HCV (acute hepatitis C with or without hepatic coma, *International Classification of Diseases, Ninth Revision* [ICD-9] code 070.41 or 070.51). For comparison and assessment of possible preferential coding for acute HCV for patients with new diagnoses, analysis was also performed for primary hospital discharge diagnoses for hepatitis, acute or chronic (ICD-9 codes 571.x, 573.x, and 070.x, excluding known alcoholic or toxic hepatitis or sequelae of chronic liver disease). Claims for diabetes (250.x) were extracted as per previous studies. We assessed the first Medicare claim for HCV or *de novo* posttransplantation diabetes. Two or more claims were required for physician supplier claims, one code for institutional claims, as per previous reports (13,14). Medicare claims for HCV occurring within 14 d after the date of transplantation were thought unlikely to represent truly incident HCV and were considered not to indicate posttransplantation HCV for purposes of this analysis.

Survival Times

Time to a Medicare claim (for either HCV or diabetes) was calculated as the time from the date of transplantation until the date of the first Medicare claim (for HCV or diabetes, respectively) during the study period, with recipients censored at time of death, loss to follow-up, or the end of the study period (December 31, 2000, the most recent date of Medicare claims available). Such calculations required survival to receive billing for a Medicare claim and thus could not assess patients who died of sudden death or undiagnosed infection. Time to Medicare claims were censored at 3 y because Medicare coverage ends 3 y after kidney transplantation unless a patient maintains coverage as a result of disability or age, which would lead to nonrandom censoring beyond 3 y. Time to death was defined as time from the date of transplantation until the date of death, censored for the end of the study period (in this case, September 30, 2001, the most recent reliable date of death) or loss to follow-up.

Life-Year Projections

The average expected number of life-years through 20 y posttransplantation in a patient cohort were estimated using methods developed previously (17–20). Briefly, expected life-years after transplantation are the area under the posttransplantation patient survival functions. The observed survival functions were used through 5 y posttransplantation. Survival functions, or death rates, were projected from 5 to 20 y posttransplantation assuming exponential functional form, a constant hazard of death between 3 and 20 y posttransplantation. The importance of the exponential assumption was tested by assuming instead a constant number of deaths, or "straight line" survival functions, each year between years 3 and 20, one of the most extreme constantly accelerating hazard models. This straight-line model produced harsh expectations, predicting that almost every patient dies $<$20 y posttransplantation. However, the primary results of interest, the proportion of life-years lost associated with posttransplantation diabetes or posttransplantation hepatitis, showed less than a 10% difference in each case between the exponential and straight-line models. Estimates of the effect on expected life-years from patients who developed posttransplantation diabetes or posttransplantation hepatitis were derived by comparing overall life-year expectations with those estimated after censoring patients at the diagnosis of posttransplantation diabetes or posttransplantation hepatitis.

Independent Variables

Patient characteristics and treatment factors were those at the date of transplantation, with the exception of comorbidity and laboratory data from CMS 2728, which was obtained at the time of first treatment for ESRD, whether dialysis or transplantation (for preemptive transplant recipients). Donor and recipient HCV antibody status was as reported to the USRDS from United Network for Organ Sharing and could not be confirmed; results were presumably ELISA 3 based on the years of the study, although some overlap with ELISA 2 could not be excluded. Further confirmatory studies, such as HCV RNA, recombinant immunoblot assay (RIBA), and liver histology, were not available. The USRDS information on maintenance immunosuppressive medications did not include total dose. Information on or response to interferon treatment was not known. The duration of dialysis before transplantation was defined as the time from the first recorded treatment for dialysis therapy until the date of transplantation. Other variables assessed included donor and recipient age, race, gender, weight, body mass index (calculated from height and weight), induction and maintenance immunosuppressive medications, graft loss, previous transplant, delayed graft function, network, state of transplant, duration of dialysis before transplantation, and allograft rejection in the first year. Diabetes was assessed as a cause of ESRD at the time of transplantation. Treatment with peritoneal dialysis for any 60-d period before transplantation was obtained from patient treatment files. Data from CMS Form 2728 was available for more than half of the cohort (see Table 1) whose first date of ESRD was on or after April 1, 1995, as a result of time elapsed from presentation to ESRD until kidney transplantation, therefore disproportionately in-

Table 1. Factors associated with HCV after kidney transplantation, kidney transplant recipients, January 1, 1996, through July 31, 2000, with Medicare as primary payer[a]

			Patients with Factor Who Had	
	N (%) or Mean ± SD	Missing (N [%])	PTHCV[b] (Incident HCV Claims after Transplantation)	PTD[c] (Excluding Patients with Prevalent Diabetes; *N* = 17,572)
N	28,924		143 (0.5)	4171 (26.2)
Donor/recipient HCV pairs		2695 (9.3)		
D+/R−	187 (0.7)		17 (9.1)[d]	49 (43.8)[d]
D+/R+	365 (1.4)		23 (6.3)[d]	104 (46.6)[d]
D−/R+	1477 (5.6)		35 (2.4)[d]	293 (32.3)[d]
D−/R−	24,200 (92.3)		54 (0.2)(Ref)	3725 (25.4)(Ref)
Demographic factors				
male recipient (*versus* female)	17,739 (59.9)	0	108 (0.6)[d]	
			HCV[b] (*n* [%])	
black recipient (*versus* all other races)	8031 (27.1)	0	62 (0.8)[d]	
mean age (y, risk per older year)	45.4 ± 14.6	0	49.7 ± 11.9[e]	
Years of dialysis before transplantation				
mean	4.09 ± 3.97	1074 (3.6)	3.46 ± 3.00	
body mass index (kg/m^2)	25.7 ± 24.8	4906 (16.6)	26.5 ± 5.4[e]	
history of PD (*versus* HD)	9942 (33.6)	Presumed 0	34 (0.3)[d]	
transfusion before transplantation (Y/N)	15,712 (54.4)	Presumed 0	74 (0.7)[d]	
Cause of ESRD				
Diabetes	7145 (28.2)	4220 (14.3)	45 (0.6)[d]	
Transplant-related factors				
Donor age (y)	36.4 ± 16.1	2616 (8.8)	38.2 ± 14.2[e]	
graft loss (*versus* continued graft function)	2025 (6.8)	Presumed 0	23 (1.2)[d]	
cadaveric donor (*versus* living donor)	22,896 (77.4)	0	130 (0.6)[d]	
kidney-liver transplant (*versus* all other transplant types)	100 (0.3)	0	4 (4.0)[d]	
pump used for donor kidney	2584 (12.0)	7352 (25.4)	15 (0.6)	
dialysis in the first week posttransplantation (delayed graft function *versus* absence of delayed graft function)	6494 (22.1)	198 (0.7)	44 (0.7)[d]	
previous transplant (*versus* primary transplant)	3857 (13.2)	293 (1.0)	7 (0.2)[d]	
donor history of alcohol use	3973 (18.8)	7753 (26.8)	33 (0.8)[d]	
donor history of illicit drug use	258 (1.2)	7606 (26.3)	34 (0.9)	
Induction immunosuppression				
induction thymoglobulin	726 (2.5)	Presumed 0	5 (0.7)	
induction OKT3	4424 (15.3)	Presumed 0	10 (0.2)[d]	
induction IL-2 antibody (daclizumab or basiliximab)	7030 (24.3)	Presumed 0	39 (0.6)	
induction methylprednisolone	18,648 (64.5)	Presumed 0	92 (0.5)	
Immunosuppression at discharge				
cyclosporine	14,037 (48.5)	Presumed 0	74 (0.5)	
tacrolimus	7526 (26.0)	Presumed 0	46 (0.6)	
azathioprine	4641 (16.0)	Presumed 0	14 (0.3)[d]	
mycophenolate	13,678 (47.3)	Presumed 0	63 (0.5)	
sirolimus	1036 (3.6)	Presumed 0	6 (0.6)	
thymoglobulin	41 (0.1)	Presumed 0	0	
OKT3	371 (1.3)	Presumed 0	0	
prednisone	27,423 (94.8)	Presumed 0	133 (0.5)	
Baseline laboratory value or history of condition in previous 10 y				
alcohol use (*versus* absence)	156 (0.9)	12,622 (42.6)	4 (2.6)[d]	
drug abuse	105 (0.6)	12,622 (42.6)	4 (3.8)[d]	
smoking (*versus* nonsmoking)	892 (5.8)	12,622 (42.6)	11 (1.1)[d]	
hematocrit (%)	28.1 ± 5.8	13,757 (46.5)	27.7 ± 5.6[e]	
serum albumin (gm/dl)	3.4 ± 0.7	15,919 (53.8)	3.2 ± 0.7	

[a] Data are the number (% of total) or mean ± 1 SD. Dates for kidney transplant recipients were January 1, 1996, through July 31, 2000, censored at 3 y of follow-up. Associations with PTD are not shown for factors other than HCV sero-pairing. For PTD, these associations have already been shown in this population and were not different in this analysis. HCV, hepatitis C virus; PTHCV, posttransplantation HCV; PTD, posttransplantation diabetes; PD, peritoneal dialysis; HD, hemodialysis; NS, nonsignificant.

[b] The percentages in the column represent the percentage of patients with each donor/recipient HCV serology combination who developed acute hepatitis C after transplantation.

[c] Analysis limited to patients without a history of diabetes before transplantation ($N = 17,572$). The percentages in the column represent the percentage of patients with each donor/recipient HCV serology combination who developed new-onset diabetes after transplantation.

[d] $P < 0.05$ *versus* patients without HCV by χ^2. In the case of donor/recipient HCV status, D−/R− is the reference group.

[e] $P < 0.05$ *versus* patients without HCV by *t* test.

cluding recipients of living donor kidneys. Because posttransplantation HCV was an early event predominantly and the USRDS did not specify exact dates of allograft rejection (only episodes that occurred within a broad time period), we were unable to establish a temporal relationship between posttransplantation HCV and allograft rejection.

Statistical Analyses

All analyses were performed using SPSS 11.5 TM (SPSS, Inc., Chicago, IL). Files were merged and converted to SPSS files using DBMS/Copy (Conceptual Software, Houston, TX). Univariate analysis of factors associated with Medicare claims for HCV or diabetes was performed with χ^2 testing for categorical variables (Fisher exact test used for violations of Cochran's assumptions) and t test for continuous variables (Mann-Whitney test was used for nonnormally distributed variables). Statistical significance for univariate comparisons was defined as $P < 0.05$. Variables with $P < 0.10$ in univariate analysis for a relationship with development of a first Medicare claim for HCV or diabetes were entered into multivariate analysis as covariates, because of the possibility of negative confounding. Variables that were thought to have a known clinical reason to be associated with HCV or diabetes were introduced into multivariate models even when univariate P values were >0.10, in accordance with established epidemiologic principles. Continuous variables were explored, and values that were thought to be inconsistent with clinical experience were excluded (set to missing). The independent association between patient factors and Medicare claims for HCV or diabetes was examined using multivariable analysis with stepwise Cox regression (likelihood ratio method) for time until the first Medicare claim for HCV or diabetes during the study period, controlling for variables entered into the model as above. Both formal and graphical methods were used to verify the existence of proportional hazards. Multivariate analysis excluded all patients with missing values, resulting in substantially smaller models than the entire study population. Sensitivity analysis was also performed substituting the mean values for missing values of continuous variables and indicator values for missing values of categorical variables in multivariate analyses, for validation purposes. Continuous variables that were nonnormally distributed were also assessed by quartiles. Hierarchically well-formed models were used for the assessment of interaction terms. No interactions higher than two-way were assessed.

Results

Of 59,077 recipients of kidney transplants from January 1, 1996, through July 31, 2000, 29,597 had valid follow-up times and evidence of Medicare as primary payer at the time of transplantation. Of these, 28,942 (97.7%) had Medicare payment dates with valid Medicare as primary payer status within 14 d of transplantation. HCV ELISA was used to determine both recipient and donor HCV status. In comparison, information on HCV RNA was available for only 0.3% of recipients, and information on HCV RIBA was available for only 1.7% of recipients. Information on HCV RNA was available for 2.2% of living donors and on HCV RIBA for 19.6% of living donors (no information available for deceased donors). Differences between patients with Medicare as primary payer and other kidney transplant recipients were as previously reported (13,14).

Demographics of the study population and rates of HCV are shown in Table 1. In unadjusted analysis, donor and recipient HCV status was directly related to the risk of posttransplantation HCV. In addition, older recipient and donor age, male recipient, black recipient, higher body mass index, diabetes, deceased donor, and pretransplantation transfusions were associated with significantly higher rates of HCV. Previous transplantation and increased duration of dialysis before transplantation were significantly associated with a lower risk of posttransplantation HCV. Among comorbid conditions at the time of presentation to ESRD from CMS Form 2728, a history of alcohol use, drug abuse, and tobacco use was significantly associated with HCV. Of note, donor kidney pump (pulsatile) perfusion (performed for deceased donors only) was performed in just over 10% of all deceased donors and was no more common among patients with posttransplantation HCV or diabetes. Specifically, pump perfusion was used in only 7.7% of DHCV+ kidneys, significantly less than for DHCV− kidneys (12.1%; odds ratio, 0.61; 95% confidence interval [CI], 0.45 to 0.83; $P = 0.002$ by χ^2).

The time to HCV, stratified by donor and recipient HCV antibody status, is shown as a Kaplan-Meier plot in Figure 1. The peak risk of HCV occurred in the first 6 mo after kidney transplantation and was highest for D+/R− (equivalent to D+/R+ for the first 6 mo), with an intermediate risk for D−/R+ and the lowest risk for D−/R−. Every category of donor and recipient HCV antibody status was significant compared with D−/R− ($P < 0.01$ by log rank test). This pattern was the same regardless of whether codes for acute or chronic hepatitis C were used. A similar pattern emerged for time to a hospitalization with a primary discharge diagnosis of hepatitis, acute or chronic.

Time to posttransplantation diabetes is shown in Figure 2.

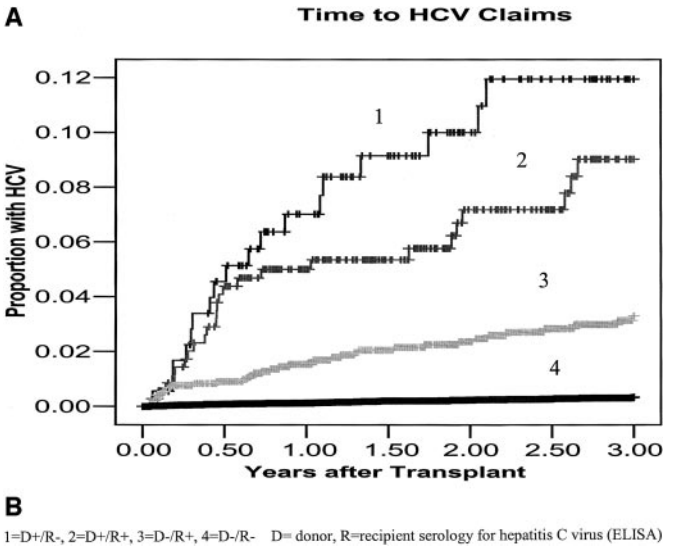

Figure 1. Time to posttransplantation Medicare claims for hepatitis C virus (HCV), U.S. kidney transplant recipients, January 1, 1996, through July 31, 2000, with Medicare as primary payer ($n = 28,924$), by category of donor/recipient HCV status. The peak risk of HCV was similar in the first 6 mo after transplantation for D+/R− (1) and D+/R+ (2), but afterward, risk decreased for D+/R+ in comparison with D+/R−. The risk for D−/R+ (3) was intermediate although still highest in the first 6 mo, with the lowest risk of all for D−/R− (4).

This analysis was limited to 17,572 recipients after excluding those with a known history of diabetes or a Medicare claim date for diabetes before the date of transplantation. As shown, donor HCV+ status was associated with higher risk of posttransplantation diabetes, regardless of recipient HCV status. D+/R+ actually had the highest rate of posttransplantation diabetes initially, whereas D+/R− rates were identical after 1 y posttransplantation. Rates for D−/R+ were substantially lower, whereas those for D−/R− were lowest of all. Almost 50% of recipients of DHCV+ kidneys developed diabetes by 3 y posttransplantation, in contrast to 25% of D−/R−.

Table 2 shows results of Cox regression analysis of factors that were independently associated with a shorter time to posttransplantation HCV and posttransplantation diabetes. In this analysis, the risk of donor/recipient HCV sero-pairings for posttransplantation HCV persisted in adjusted analysis. Other independent factors were transfusion history, deceased donor, shorter duration of pretransplantation dialysis, first *versus* previous transplant, history of hemodialysis (*versus* peritoneal dialysis), and male recipient. Specifically, pulsatile perfusion of deceased donor organs was not significantly associated with either time to posttransplantation HCV (AHR, 0.71; 95% CI, 0.28 to 1.79; $P = 0.47$) or posttransplantation diabetes (AHR, 1.05; 95% CI, 0.94 to 1.18; $P = 0.41$).

HCV sero-parings were also independently associated with the risk of posttransplantation diabetes, with the highest risk occurring for DHCV+ status regardless of recipient status, as indicated in Figure 2. D−/R+ patients also had a significantly higher risk of posttransplantation diabetes compared with D−/R− recipients. Other factors associated with posttransplantation diabetes were similar to those of previous reports. However, we did not find a statistically significant interaction between use of tacrolimus at discharge and HCV sero-pairings. A significant interaction was also not detected between tacrolimus and either recipient or donor HCV status when assessed separately.

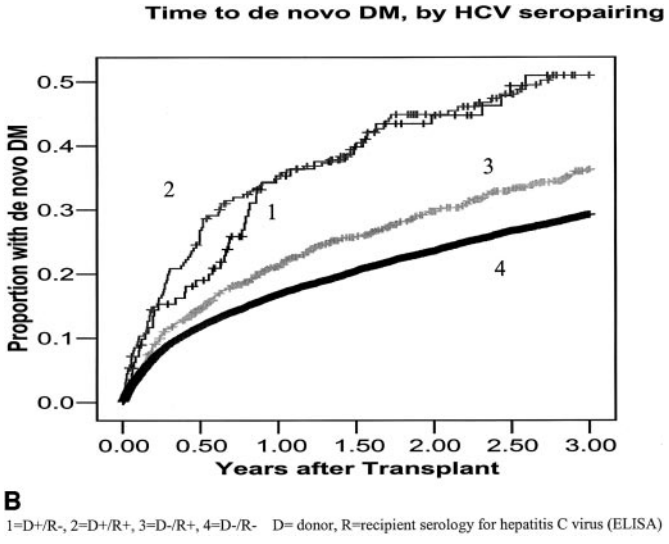

Figure 2. Time to *de novo* posttransplantation diabetes, also stratified by donor/recipient HCV status, limited to patients without known prevalent diabetes ($n = 17,572$) as in Table 1. Donor HCV+ kidneys were independently associated with a higher risk of posttransplantation diabetes (with a risk of almost 50% at 3 y posttransplantation), regardless of recipient status. More than one third of cases of posttransplantation diabetes occurred in the first 6 mo, and >50% of cases by 1 y, at 3 y of maximum follow-up.

One-year survival was 84% among patients after the diagnosis of posttransplantation hepatitis, 91% after diagnosis of posttransplantation diabetes, and 94% for the entire cohort. In time-dependent Cox regression, posttransplantation HCV was independently associated with an increased risk of death (AHR, 3.36; 95% CI, 2.44 to 4.61) as was posttransplantation diabetes (AHR, 1.81; 95% CI, 1.54 to 2.11; Table 3). Specified causes of death were missing for 43% of patients with Medicare claims for HCV posttransplantation. The leading specified causes of death were cardiovascular (19.5%), infection (19.5%), and due to liver disease (17.1%). In comparison, the leading causes of death among patients without Medicare claims for HCV were cardiovascular disease (22.4%) and infection (12.4%); liver disease accounted for 1.6% of deaths. Statistical analysis was not performed because of the high percentage of missing values. Causes of death were not substantially different for patients with posttransplantation diabetes except for a lower incidence of liver disease (cardiovascular in 18.0%, infection in 12.4%, liver disease in 1.7%). Among DHCV+ patients with posttransplantation diabetes, 63.9% of causes of death were missing. The leading specified causes of death were cardiovascular disease (11.1%) and infection (8.3%), whereas no deaths as a result of liver disease were reported in this group.

Table 4 shows average expected life-years after kidney transplantation, stratified by donor/recipient HCV serology and by the development of posttransplantation diabetes or posttransplantation hepatitis, respectively. Expected life-years were higher in stepwise manner by donor and recipient HCV status. Censoring patients at the development of posttransplantation diabetes was associated with improved survival, most pronounced in the D−/R+ patients. In contrast, censoring at posttransplantation hepatitis had a minimal impact on survival except for D+/R+ patients. In every category and expressed as a percentage of life-years lost relative to HCV sero-matched recipients of HCV sero-negative kidneys who developed neither posttransplantation diabetes nor posttransplantation hepatitis, the development of posttransplantation diabetes had a much greater impact on survival than posttransplantation hepatitis. Among recipients of HCV+ donor kidneys, posttransplantation diabetes was associated with almost 50% of life-years lost, compared with <10% for posttransplantation HCV.

Discussion

The present study found that posttransplantation diabetes was much more commonly associated with use of DHCV+ kidneys than posttransplantation HCV. Whereas the relative risk of death was higher after posttransplantation hepatitis than posttransplantation diabetes, posttransplantation diabetes was much more common and therefore was associated with a greater share of total mortality and years of life lost than

Table 2. Cox regression analysis of factors independently associated with new HCV and PTD occurring after kidney transplantation[a]

	AHR for HCV	AHR for PTD
Donor/recipient HCV pairs		
D+/R−	35.4 (19.9–63.1)	1.69 (1.19–2.39)
D+/R+	24.9 (14.7–42.2)	1.76 (1.37–2.26)
D−/R+	11.1 (7.1–17.5)	1.26 (1.07–1.49)
D−/R− (Reference)	1	1
Other factors		
transfusion before transplantation	1.58 (1.09–2.28)	NS
previous transplant	0.23 (0.08–0.63)	0.59 (0.52–0.67)
black recipient	NS	1.47 (1.34–1.60)
BMI (per higher quartile)	1.20 (1.01–1.44)	1.29 (1.25–1.35)
years of pretransplantation dialysis (per quartile)	0.55 (0.46–0.67)	NS
deceased donor kidney	1.84 (1.01–3.37)	NS
male recipient	1.63 (1.08–2.46)	NS
tacrolimus use at discharge	NS	1.49 (1.35–1.63)
age (per higher quartile)	NS	1.37 (1.32–1.43)
HLA mismatch (per mismatch)	NS	1.04 (1.02–1.07)
diabetes	1.68 (1.15–2.44)	Excluded

[a] Data given as the number (% of total) or mean ± 1 SD. Dates for kidney transplant recipients were January 1, 1996, through July 31, 2000, censored at 3 y of follow-up. AHR, adjusted hazard ratio; BMI, body mass index.

Table 3. Association of *de novo* hepatitis and *de novo* diabetes with mortality after kidney transplantation

	AHR for Mortality[a] (95% CI)	*P* Value
Posttransplantation Hepatitis C	3.36 (2.44–4.61)	<0.001
Posttransplantation diabetes	1.81 (1.54–2.11)	<0.001

[a] As time-dependent variables. Other variables in the model were donor and recipient age, diabetes, PD, cadaver donor, donor CMV+, and duration of dialysis before transplantation.

Table 4. Life-years by HCV sero-pairing and posttransplantation diabetes and hepatitis, respectively

Life-Years	Overall	Censored at PTD	Censored at PTHCV	Life-Years Lost (Total)		Life-Years Lost (%)	
				Associated With PTD	Associated With PTHCV	% as a Result of PTD	% as a Result of PTHCV
D+/R−	11.12	16.6	11.04	5.48	−0.08	49.3%	−0.7%
D+/R+	11.51	16.91	12.33	5.4	0.82	46.9%	7.1%
D−/R+	15.86	22.07	15.86	6.21	0	39.2%	0.0%
D−/R−	19.84	22.25	19.87	5.41	0.03	27.3%	0.2%

posttransplantation hepatitis, particularly among recipients of DHCV+ kidneys. Previous studies of DHCV+ kidneys have focused on the development of posttransplantation hepatitis (6,7), much as studies of CMV have focused on CMV disease after kidney transplantation (8–11). Although recipient HCV status has a well-established association with the development of *de novo* diabetes (13,14,21,22), the potential role of posttransplantation diabetes in outcomes associated with use of DHCV+ kidneys, although logical by extrapolation, has not been previously investigated.

In the present study, posttransplantation diabetes occurred early after transplantation, was common (occurring in almost 50% of recipients of HCV+ donor kidneys, regardless of recipient HCV status at 3 y), was independently associated with an increased risk of mortality [consistent with previous studies (13,14)], and was associated with a much larger share of years of life lost than posttransplantation hepatitis. Posttransplantation diabetes therefore may be at least one potential mechanism for the increased risk of mortality associated with the use of DHCV+ kidneys (1,2). Our findings suggest that

acute infection/transmission of HCV (as seen in patients who received a DHCV+ kidney, regardless of recipient status) may be associated with a higher risk for posttransplantation diabetes than for HCV+ recipients who received DHCV− kidneys (D−/R+). D−/R+ patients may have received treatment before transplantation, thus possibly achieving a higher rate of remission, and also would not have been reexposed to HCV after transplantation. Consistent with this hypothesis, Gursoy *et al.* (23) reported that treatment of HCV disease has been associated with a reduced incidence of posttransplantation diabetes, and others have reported on a lower incidence of posttransplantation glomerulonephritis after pretransplantation treatment of HCV-positive recipients (24), suggesting that pretransplantation antiviral treatment of HCV disease may have wider benefits than just direct treatment of disease.

Most reviews of the kidney transplant literature agree that posttransplantation HCV is more morbid than HCV acquired before transplantation. It has been assumed this is due to the difficulty of treatment for HCV infection after kidney transplantation as a result of the increased risk of allograft rejection associated with interferon therapy (25,26). Therefore, treatment of HCV+ recipients is strongly recommended before transplantation (27,28). Expert recommendations limit use of DHCV+ kidneys to recipients who are HCV RNA positive, *i.e.*, those who still have active infection, because responders seem to have an excellent long-term prognosis after transplantation (29). It was not possible to determine whether expert recommendations are being followed nationally, because we had no information on response to treatment or HCV RNA status pretransplantation. Compliance may be low because it has been assumed that use of DHCV+ kidneys in this setting had minimal adverse effects because there would be a long time from the date of infection until the manifestations of clinical disease, assumed to be liver disease. The present study challenges these assumptions, which is unfortunate because effective, relatively nontoxic prophylaxis and treatment for HCV after transplantation is not available, in contrast to other viral infections such as CMV. Patients with HCV genotype 1, the most common genotype in the United States, must generally undergo a 48-wk course of therapy with combination pegylated interferon and ribavirin (30), resulting in remission in 50% at best. Consequently, even under the best of circumstances, HCV+ transplant candidates who undergo treatment may incur a prolonged wait before transplantation in comparison with HCV-recipients [an association well documented in the literature (2,31)], with no guarantee of remission beforehand. The present study's findings of an association between both increasing time on dialysis and repeat transplantation with a *lower* frequency of *incident* (not prevalent) posttransplantation HCV suggests that patients who develop HCV disease while on dialysis may be less likely to receive a repeat transplant, perhaps as a result of complications of their disease or its treatment, which is also consistent with previous reports (32).

Given the difficulty of treating HCV disease both before and after transplantation, the findings of the present study highlight the increased importance of preventing HCV viral transmission in the first place. Although testing of donor kidneys for HCV RNA or genotype before transplantation is not currently practical because of time constraints, effective means of reducing viral transmission are available. In 1994, Zucker *et al.* (33) reported that using pulsatile perfusion, >99% of HCV virus could be eliminated from the donor kidney. Although the long-term outcomes of using pulsatile perfusion for DHCV+ kidneys are not known, it seems to be a promising approach to this problem. Unfortunately, we found that pulsatile perfusion is underutilized in DHCV+ kidneys in the US renal transplant population, presumably because of cost and the unfortunately still common attitude that viral transmission of HCV by donor kidneys is only a concern for late complications, an assumption that is not supported by the weight of current evidence.

This study has several limitations, similar to previous studies (1,2). Outcomes could not be verified independently. We had no access to liver biopsy or other invasive diagnostic tests. The full range of clinical manifestations of posttransplantation HCV and posttransplantation diabetes, other than their apparent adverse association with survival, could not be determined. Previous studies have shown that whether the donor or recipient HCV viral strain predominates after transplantation is unpredictable (34). Because of the lower prevalence but higher virulence of HCV in the United States compared with other countries (35), results of the present analysis may not be applicable outside the United States. All outcomes assessed in the present study are likely insensitive. In particular, clinical diabetes may be merely the "tip of the iceberg" in terms of patients who are at risk from hyperglycemia; thus, even more patients may be affected than indicated in this analysis. Even hyperglycemia short of clinical diabetes has been implicated in early mortality in critically ill patients (36), as well as with atherosclerosis.

In conclusion, analysis of the U.S. kidney transplant population indicates that posttransplantation diabetes is far more commonly associated with use of DHCV+ kidneys than is posttransplantation hepatitis. Although both outcomes occurred early and were independently associated with an increased risk of death, posttransplantation diabetes accounted for more years of life lost than posttransplantation hepatitis, particularly among patients who received DHCV+ kidneys. The findings of the present study suggest that more could be gained by focusing on posttransplantation diabetes as an outcome than posttransplantation liver disease among kidney transplant patients who are affected by HCV. In particular, early steroid avoidance/withdrawal, which was not common during the study period, has shown promise in preliminary studies of HCV+ recipients (37). Similar attention may need to be directed to recipients of DHCV+ kidneys. Because of the difficulties in treating HCV acquired after transplantation, methods that have been shown to reduce HCV viral transmission, such as pulsatile perfusion (33), warrant renewed attention.

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