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Research article

Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome after renal transplantation in the United States

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Abstract

Background: The incidence and risk factors for diabetic ketoacidosis (diabetic ketoacidosis) and hyperglycemic hyperosmolar syndrome (hyperglycemic hyperosmolar syndrome, previously called non-ketotic hyperosmolar coma) have not been reported in a national population of renal transplant (renal transplantation) recipients.

Methods: We performed a historical cohort study of 39,628 renal transplantation recipients in the United States Renal Data System between 1 July 1994 and 30 June 1998, followed until 31 Dec 1999. Outcomes were hospitalizations for a primary diagnosis of diabetic ketoacidosis (ICD-9 code 250.1x) and hyperglycemic hyperosmolar syndrome (code 250.2x). Cox Regression analysis was used to calculate adjusted hazard ratios for time to hospitalization for diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome.

Results: The incidence of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome were 33.2/1000 person years (PY) and 2.7/1000 PY respectively for recipients with a prior diagnosis of diabetes mellitus (DM), and 2.0/1000 PY and 1.1/1000 PY in patients without DM. In Cox Regression analysis, African Americans (AHR, 2.71, 95 %CI, 1.96–3.75), females, recipients of cadaver kidneys, patients age 33–44 (vs. >55), more recent year of transplant, and patients with maintenance TAC (tacrolimus, vs. cyclosporine) had significantly higher risk of diabetic ketoacidosis. However, the rate of diabetic ketoacidosis decreased more over time in TAC users than overall. Risk factors for hyperglycemic hyperosmolar syndrome were similar except for the significance of positive recipient hepatitis C serology and non-significance of female gender. Both diabetic ketoacidosis (AHR, 2.44, 95% CI, 2.10–2.85, $p < 0.0001$) and hyperglycemic hyperosmolar syndrome (AHR 1.87, 95% CI, 1.22–2.88, $p = 0.004$) were independently associated with increased mortality.

Conclusions: We conclude that diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome were associated with increased risk of mortality and were not uncommon after renal transplantation. High-risk groups were identified.

Background

Renal transplant recipients are at high risk for post-transplant diabetes mellitus. However, information on the incidence and risk factors for diabetic ketoacidosis (diabetic ketoacidosis) after solid organ transplantation has been limited to single-center reports. [1–4] There are even fewer reports on hyperglycemic hyperosmolar syndrome (hyperglycemic hyperosmolar syndrome, previously called nonketotic hyperosomolar coma) after renal transplantation. [5,6] Recently, post-transplant diabetes mellitus has been associated with tacrolimus use in renal transplant recipients with hepatitis C antibody positivity, [7] although this experience is not universal. [8] Only one report of diabetic ketoacidosis associated with tacrolimus use in a patient without a prior history of diabetes has so far been reported. [9] Tacrolimus was approved by the FDA for use in kidney transplantation in 1997. We therefore performed a historical cohort study of the United States Renal Data System (USRDS) Renal transplant population. Our objectives were to determine the incidence, risk factors, and mortality associated with hospitalizations for diabetic ketoacidosis (primary hospitalization discharge ICD9 code 250.1x) and hyperglycemic hyperosmolar syndrome (ICD9 code 250.2x) occurring after renal transplantation.

Methods

Patient Population

This study used data from the United States Renal Data System (USRDS), using standard analysis files (SAF's) as of May 2000. The USRDS, indirectly mandated by federal law, incorporates baseline and follow-up demographic and clinical data on all patients receiving end stage renal disease (ESRD) therapy in the United States. ESRD therapy includes hemodialysis, peritoneal dialysis, and renal transplantation. Because patient entry into the USRDS is linked to Medicare reimbursement, and ESRD services are expensive, very few transplant patients are not represented in the database. The variables included in the USRDS standard analysis files (SAF), as well as data collection methods and validation studies, are listed at the USRDS website, under 'Researcher's Guide to the USRDS Database', Section E, 'Contents of all the SAF's, http://www.usrds.org and published in the USRDS. The demographics of the renal transplant population have been previously described (2001 USRDS report). SAF.TXUNOS was used as the primary dataset, and merged with variables from SAF.HOSP for hospitalization data, and SAF.PATIENTS for dates and causes of death as well as causes of renal disease, as previously reported. [10–12] Patient characteristics and treatment factors were those at the date of transplant. Recipients of organs other than kidneys were excluded.

Outcome Definition

We conducted a historical cohort study of the incidence, risk factors and associated patient survival for hospitalized cases of diabetic ketoacidosis (based on International Classification of Diseases-9th Modification Diagnosis Codes (ICD9) at hospital discharge for diabetic ketoacidosis, 250.1x, and hyperosmotic hyperosmolar syndrome (also known as non-ketotic hyperosmolar coma), ICD9 code 250.2x, as a primary discharge diagnosis in renal transplant recipients. The first hospitalization for diabetic ketoacidosis after the first solitary renal transplant (thus excluding kidney-pancreas or other multiple transplants) for a given individual occurring on or after 1 July 1994 and before 1 July 1998 (which included repeat transplants), with follow-up time truncated at three years was counted in analysis. Hospitalizations were chosen because they were more accessible in the database and less subject to interpretation than outpatient cases of diabetic ketoacidosis, especially since the USRDS database has no information on confirmatory studies. Hospitalization data for transplant recipients may be unreliable after the patient has survived ≥ 3 years post transplant, when hospitalization reporting to Medicare for patients 65 years or younger is no longer required. However, Medicare reporting starts immediately after transplant, regardless of preceding dialysis status. All hospitalizations with a primary discharge diagnosis for diabetic ketoacidosis were extracted from SAF.HOSP, merged with the transplant file using unique identifiers, and hospitalizations outside the range of the study period were excluded. Hospitalizations for diabetic ketoacidosis occurring at any time after renal transplant, including after graft failure (censored for patient death), were counted in analysis.

Variables used in analysis

The independent associations between patient factors and hospitalizations for diabetic ketoacidosis were examined using multivariate analysis with stepwise Cox Regression including recipient and donor age, recipient race, gender, weight, pretransplant dialysis (yes/no), duration of dialysis prior to transplantation, total follow-up time, recipient hepatitis C serology, donor cytomegalovirus serology, pre-transplant dialysis (yes/no), rejection (either treatment or diagnosis) occurring at any time in the study period, induction antibody therapy, maintenance

Table 1: Rates of Diabetic Ketoacidosis

	Diabetic ketoacidosis	No diabetic ketoacidosis	Mean followup (years)	Rate per 1000 PY
By Total Hospitalizations				
Diabetes at listing[A] "Recurrent"	505	7733	1.80 ± 1.11	33.22
No Diabetes at listing "De novo"	84	24,232	1.76 ± 1.07	1.96
By Recipients Hospitalized[B]				
Diabetes at listing[A] "Recurrent"	244	7733	1.80 ± 1.11	16.99
No Diabetes at listing "De novo"	75	24,232	1.76 ± 1.07	1.75

Numbers and rates (per 1000 person years (PY) of followup) for renal transplant recipients in the US, 1 July 1994–30 June 1998, limited to patients with valid information for diabetes as a comorbidity at the time of listing for renal transplantation ([A]). 23.3% of patients had unknown or missing values for this variable. Factors associated with missing values for this variable are given in the results section. diabetic ketoacidosis=Primary Hospital Discharge Diagnosis for diabetic ketoacidosis during the study period [A]Diabetes as a comorbid condition at the time of listing for transplant. [B] No duplicate hospitalizations, only one hospitalization per patient "Recurrent" refers to hospitalized diabetic ketoacidosis occurring in patients with a known prior diagnosis of diabetes as a comorbid condition. We did not use diabetes as a cause of renal failure to make this distinction, since that would most likely underestimate renal transplant recipients who actually had diabetes. "De novo" refers to hospitalized diabetic ketoacidosis occurring in patients WITHOUT a known prior diagnosis of diabetes as a comorbid condition. Patients with medication induced diabetic ketoacidosis of hyperglycemic hyperosmolar syndrome would fall into this category.

Table 2: Rates of Non-Ketotic Hyperosmolar Coma

	Hyperglycemic hyperosmolar syndrome	No Hyperglycemic hyperosmolar syndrome	Mean followup (years)	Rate per 1000 PY
By Total Hospitalizations				
Diabetes at listing[A]	39	7943	1.80 ± 1.11	2.7
No Diabetes at listing	49	24,259	1.76 ± 1.07	1.1
By Recipients Hospitalized[B]				
Diabetes at listing[A]	34	7943	1.80 ± 1.11	2.4
No Diabetes at listing	48	24,259	1.76 ± 1.07	1.1

Numbers and rates (per 1000 person years (PY) of followup) for renal transplant recipients in the US, 1 July 1994–30 June 1998. hyperglycemic hyperosmolar syndrome=Primary Hospital Discharge Diagnosis for non-ketotic hyperosmolar coma during the study period [A]Diabetes as a comorbid condition at the time of listing for transplant. 23.3% of patients had unknown or missing values for this variable. Factors associated with missing values for this variable are given in the results section. [B] No duplicate hospitalizations, only one hospitalization per patient

immunosuppressive medications at time of discharge after transplant surgery, graft loss, and cause of end stage renal disease (ESRD, either diabetes or other causes). The USRDS does not reliably distinguish between type I and type II diabetes. Previous investigators have used the occurrence of diabetes in patients younger than age 40 as a surrogate for type I diabetes. (13) However, given the growing frequency of type II diabetes in younger patients, (14) we did not think this assumption would be valid in more recent years of the database. We therefore chose to group all patients with ESRD due to diabetes together. Diabetes as a comorbid condition at the time of listing for transplant was also used as a variable, although information on this variable was missing or unknown for 23.3% of patients (Tables 1,2,3). Information on insulin dependence was missing for 81% of patients, however, and was not considered reliable for analysis. Episodes of rejection were not restricted to those occurring in the first year, in contrast to studies of allograft function, since there is no evidence that late (vs. early) rejection has a different impact on diabetic ketoacidosis. However, only episodes of diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome occurring after the approximate date of rejection were used in assessing the association of rejection with diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome. The total cumulative dose of prednisone was not

available in the USRDS. UNOS tracks the numbers of days of prednisone administered prior to initial hospital discharge; however, values were missing for >90% of patients in both databases and could not be used as a covariate in the above analyses. Maintenance immunosuppressive medication use, in particular cyclosporine and tacrolimus, at the time of discharge after transplantation was also analyzed as a preexisting covariate. Information on use of medications (other than immunosuppressive medications), alcohol, tobacco, or radiologic procedures was not available. Dialysis modality was obtained from the file Sdiabetic ketoacidosis.RXHIST60. The initial dialysis modality a patient used for at least 60 days after presentation to end stage renal disease and prior to renal transplantation was utilized in intention to treat fashion.

Survival Times

For time to diabetic ketoacidosis, survival time was defined as the time from first renal transplant until hospitalization for diabetic ketoacidosis, with patients censored at death, loss to follow-up, or end of the study. Since the most recent hospitalization date was 31 December, 1999, this was considered the end of the study period for this measurement. Survival time was defined as the time from the date of transplant until the date of death, censored for loss to follow-up or the end of the study. The end of the study period was considered April 2000 for this measurement. The patient survival probabilities were estimated by using the Life Tables and Kaplan Meier method.

Statistical Analysis

All analyses were performed using SPSS 9.0 TM (SPSS, Inc., Chicago, IL). Files were merged and converted to SPSS files using DBMS/Copy (Conceptual Software, Houston, TX). Univariate analysis was performed with Chi-square testing for categorical variables (Fisher's exact test was used for violations of Cochran's assumptions) and Student's two-sided t-test for continuous variables (the Wilcoxon signed rank test was used for variables without a Gaussian distribution). Linear regression analysis was used to assess trends over time, with adjusted residuals inspected to verify the appropriateness of the regression technique. Variables with $p < 0.10$ in univariate analysis for a relationship with development of hospitalization for diabetic ketoacidosis were entered into multivariate analysis as covariates. Kaplan-Meier analysis was used to construct survival plots of time to hospitalized diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome after renal transplantation. Log-log plots were inspected to assess for proportionality of hazards over time at the mean of each significant covariate. Because the majority of patients were censored (did not experience the primary outcome) during the study period, stepwise Cox Regression (likelihood ratio method) was used to model factors associated with time to hospitalized diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, controlling for covariates listed above. For all risk factor analysis reported in the present study, only the first hospitalization for diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, respectively, occurring during the study period was analyzed (one hospitalization per patient). The association of hospitalized diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome was assessed using Cox non-proportional hazards regression, with times after hospitalization for diabetic ketoacidosis coded as 1 and all other times as 0, as previously reported. [15]

Tacrolimus was introduced into clinical practice more recently than cyclosporine. This could have resulted in bias due to the shorter potential follow-up for patients taking cyclosporine, leading to unequal counting of more recent hospitalizations for diabetic ketoacidosis in patients who used tacrolimus. In addition, since the rate of diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome may have changed in more recent years of the study, temporal bias could have arisen despite adjustment for year of transplant. Therefore, additional analysis was performed limited to patients who were transplanted on or after 1 January, 1996.

Results

There were 42,096 solitary renal transplant recipients in the United States Renal Data System transplanted from 1 July 1994 to 30 June 1998, of whom 39,628 had data complete enough to calculate survival times. The most recent hospitalization date was December 31, 1999. The most recent date of death was April 2000. Mean follow-up was 1.89 ± 1.15 years (median, 1.91 years). Of these, 428 recipients were hospitalized with a primary discharge diagnosis of diabetic ketoacidosis with 760 total hospitalizations. 115 recipients were hospitalized with a primary discharge diagnosis of hyperglycemic hyperosmolar syndrome with 122 total hospitalizations. The most common secondary discharge diagnosis for both diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome was kidney replaced by transplant, and secondary diagnoses did not reveal a preponderance of conditions suggesting an underlying condition leading to hospitalization. Rates of diabetic ketoacidosis by history of diabetes at the time of listing are shown in Table 1. Characteristics of the study population, as well as risk factors for diabetic ketoacidosis for the entire cohort and for recipients without a history of diabetes at the time of listing are shown in Table 2. As previously reported, the use of tacrolimus rose steadily during the study period, accounting for 5.2% of all calcineurin inhibitor use in 1994, 5.9% in 1995, 12.1% in 1996, 17.5% in 1997, and 20.3% in 1998. The three-year incidence of de novo diabetic ketoacidosis was 1.56% in patients using tacrolimus vs. 0.35% in patients using cyclosporine. However, there were noteworthy temporal

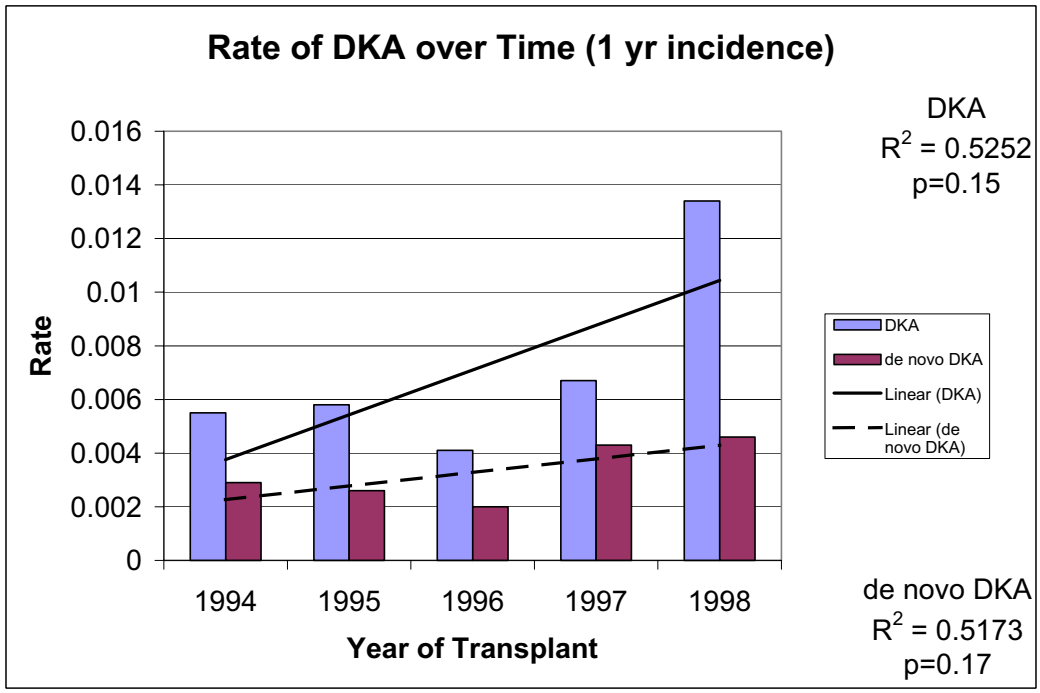

Figure 1
Rate of Hospitalizations for Diabetic Ketoacidosis (diabetic ketoacidosis, ICD9 code 250.1x) total and de novo (in patients without a history of diabetes as a comorbid condition) over the years of the study. The rate of both total and de novo diabetic ketoacidosis increased over time, although these trends were not statistically significant in linear regression analysis.

trends during the time of the study, although none were statistically significant. As shown in Figure 1, there was an increase in the rate of both all cases of diabetic ketoacidosis and de novo diabetic ketoacidosis during the years of the study. However, an opposite trend was seen in de novo diabetic ketoacidosis in tacrolimus users, Figure 2. As shown, the rate of de novo diabetic ketoacidosis decreased sharply among tacrolimus users, while the rate of total diabetic ketoacidosis did not change. Similar data for hyperglycemic hyperosmolar syndrome are shown in figures 3,4. In contrast, there were no clear trends over time, although rates for the year 1998 appeared disproportionately high.

The mean age of patients hospitalized for diabetic ketoacidosis was 41.4 ± 11.1 years vs. 43.4 ± 14.9 years for recipients not hospitalized for diabetic ketoacidosis, p = 0.006 by student's t-test (equal variances assumed). The mean BMI of patients hospitalized for hyperglycemic hyperosmolar syndrome was 24.4 ± 4.5 kg/m^2 vs. 25.2 ± 5.3 kg/m^2 for recipients not hospitalized for hyperglycemic hyperosmolar syndrome, p = 0.008 by student's t-test. Of African American recipients, 1.6% were hospitalized for diabetic ketoacidosis during the study period vs. 0.8% of recipients of other races (p < 0.001 by Chi Square), and of patients hospitalized for diabetic ketoacidosis, 37% were African American, vs. 23.1% of patients

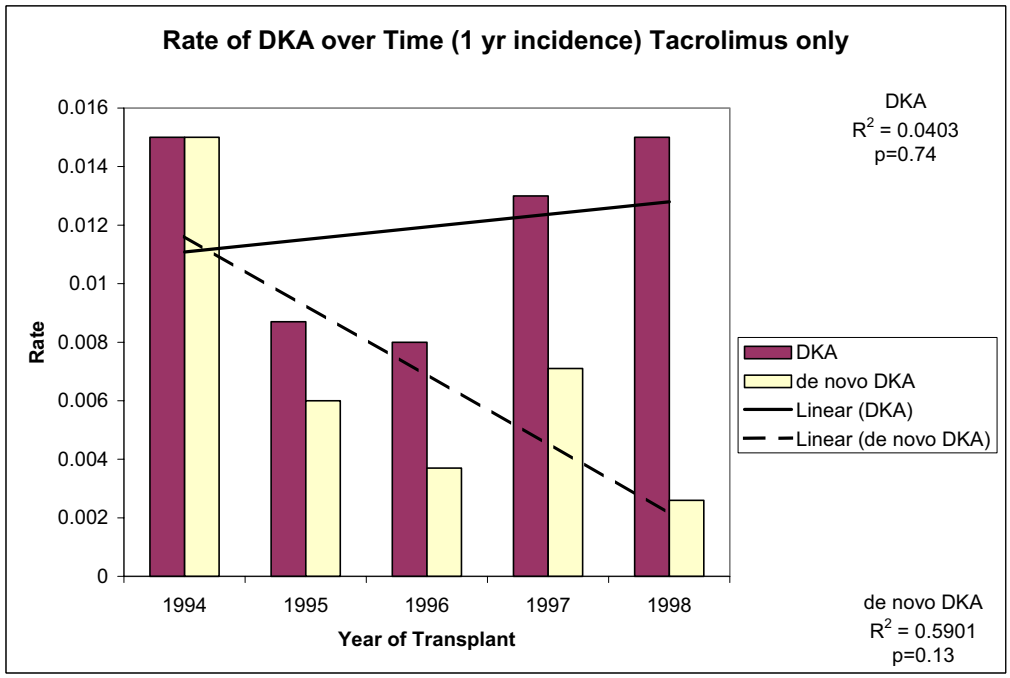

Figure 2
Rate of Hospitalizations for Diabetic Ketoacidosis (diabetic ketoacidosis, ICD9 code 250.1x) total and de novo (in patients without a history of diabetes as a comorbid condition) over the years of the study, limited to patients with baseline tacrolimus use. There was a marked **decrease** in de novo diabetic ketoacidosis over time in this group (p = 0.13 by linear regression), with no significant trend over time for total diabetic ketoacidosis.

not hospitalized for diabetic ketoacidosis ($p < 0.001$ by Chi Square).

In Cox Regression analysis, factors that were positively associated with total rates of hospitalized diabetic ketoacidosis were younger age, graft loss, African American race, more recent year of transplant, lower body mass index, and female gender. There were no significant interactions between race, gender, hepatitis C status, or tacrolimus use. For de novo diabetic ketoacidosis, gender and graft loss were not significant, and cadaver donor was significant. Recipients who used maintenance tacrolimus (adjusted hazard ratio, 2.27, 95% confidence interval, 1.52–3.38, p = 0.001) had a higher risk of de novo diabetic ketoacidosis, compared to recipients who used cyclosporine. Significance persisted even in analysis limited to patients who were transplanted on or after 1 Jan 1996 (adjusted hazard ratio for tacrolimus, 1.75, 95% confidence interval, 1.06–2.89, p = 0.03). However, the pattern of risk over time violated the proportional hazards assumption, since there was a substantially greater risk of de novo diabetic ketoacidosis among tacrolimus users starting at two years after transplant, coinciding with the introduction of tacrolimus into clinical practice. Therefore, analysis was also performed limited to patients transplanted on or after 1 July 1996, limited to two years of follow-up. In this analysis,

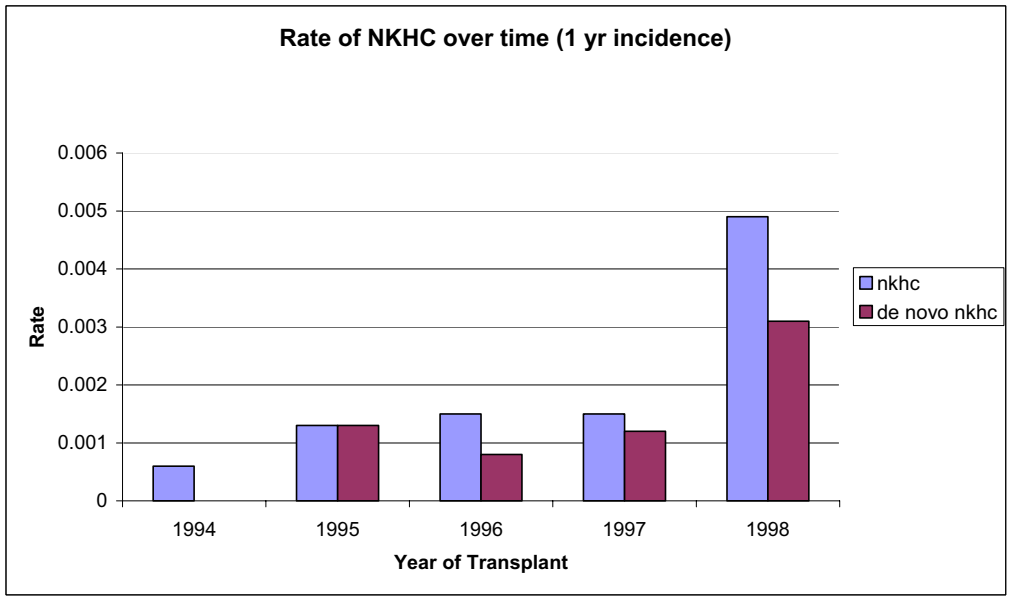

Figure 3
Rate of Hospitalizations for Hyperosmolar Hyperglycemic syndrome (hyperglycemic hyperosmolar syndrome), also known as Nonketotic hyperosmolar coma (NKHC, ICD9 code 250.2x) total and de novo (in patients without a history of diabetes as a comorbid condition) over the years of the study, entire study cohort. Results are linear regression are not shown due to lack of significance, although the year 1998 may be an outlier.

tacrolimus was not significantly associated with de novo diabetic ketoacidosis, p = 0.10, adjusted hazard ratio, 2.11, 95% CI, 0.86–5.21. In analysis including patients with diabetes during the entire study period, tacrolimus use was only significantly associated with diabetic ketoacidosis in recipients of cadaver kidneys (adjusted hazard ratio, 2.15, 95% CI, 1.10–4.23, p = 0.03).

The mean age of patients hospitalized for hyperglycemic hyperosmolar syndrome was 46.2 ± 13.0 years vs. 43.4 ± 14.9 years for recipients not hospitalized for hyperglycemic hyperosmolar syndrome, p = 0.04 by student's t-test (equal variances assumed). The mean BMI of patients hospitalized for hyperglycemic hyperosmolar syndrome was 26.6 ± 4.9 kg/m^2 vs. 25.2 ± 5.3 kg/m^2 for recipients not hospitalized for hyperglycemic hyperosmolar syndrome, p = 0.03 by student's t-test. Of recipients who were seropositive for hepatitis C, 0.8% were hospitalized for hyperglycemic hyperosmolar syndrome during the study period vs. 0.2% of HCV negative recipients (p < 0.001 by Chi Square), and of patients hospitalized for hyperglycemic hyperosmolar syndrome, 16.5% were HCV positive, vs. 5.7% of patients not hospitalized for hyperglycemic hyperosmolar syndrome (p < 0.001 by Chi Square). Of African American recipients, 0.7% were hospitalized for hyperglycemic hyperosmolar syndrome during the study

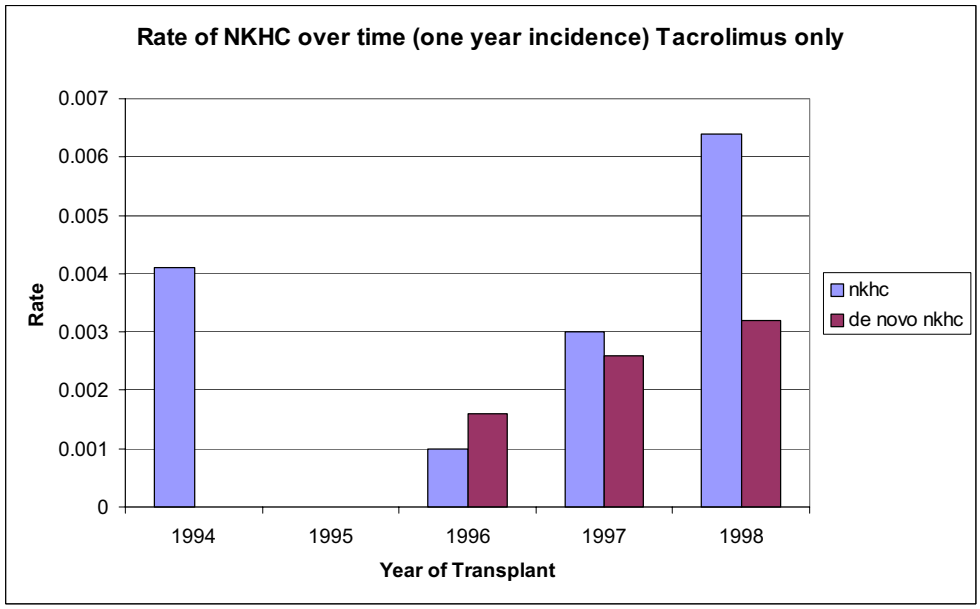

Figure 4
Rate of Hospitalizations for hyperglycemic hyperosmolar syndrome (code 250.2x) total and de novo (in patients without a history of diabetes as a comorbid condition) over the years of the study, limited to patients with baseline tacrolimus use.

period vs. 0.1% of recipients of other races ($p < 0.001$ by Chi Square), and of patients hospitalized for hyperglycemic hyperosmolar syndrome, 60% were African American, vs. 23.1% of patients not hospitalized for hyperglycemic hyperosmolar syndrome ($p < 0.001$ by Chi Square). There was considerable overlap between risk factors for diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome except for the significance of recipient hepatitis C positive serology and the lack of significance of female gender (Table 4). There was no significant interaction between recipient hepatitis C serology and tacrolimus use. There was no association between hyperglycemic hyperosmolar syndrome and BMI, either as a continuous or as a categorical variable. No independent risk factors for de novo hyperglycemic hyperosmolar syndrome were identified, and are therefore not presented in tabular form.

In-hospital mortality was 1.9% for patients with diabetic ketoacidosis and 0.9% for patients with hyperglycemic hyperosmolar syndrome. Mortality after diabetic ketoacidosis is shown in Figure 5. The risk of mortality after hospitalization for diabetic ketoacidosis was fairly constant over time. Hospitalized diabetic ketoacidosis was independently associated with increased mortality in Cox non-proportional hazards regression analysis, adjusted hazard ratio = 2.44, 95% CI, 2.10–2.85, $p < 0.0001$. Causes of death were missing or unknown for 57.3% of

Figure 5
Mortality after hospitalization for diabetic ketoacidosis (diabetic ketoacidosis). diabetic ketoacidosis was associated with a significantly increased risk of mortality after renal transplantation and was fairly constant over time. diabetic ketoacidosis was independently associated with mortality compared to renal transplant recipients who did not have diabetic ketoacidosis (by Cox non-proportional hazards regression analysis, adjusted hazard ratio = 2.44, 95% CI, 2.10–2.85, $p < 0.0001$).

patients with diabetic ketoacidosis. The leading specified causes of death were cardiac arrest of unknown cause (8.5%), acute myocardial infraction (5%), sepsis (4%), and atherosclerotic heart disease (4%).

Similar to the linear risk of mortality after diabetic ketoacidosis, the risk of mortality after hyperglycemic hyperosmolar syndrome was constant over time (Figure 6). Hospitalization for hyperglycemic hyperosmolar syndrome was independently associated with increased mortality in Cox non-proportional hazards regression analysis, adjusted hazard ratio = 1.87, 95% CI, 1.22–2.88, p = 0.004. Causes of death were missing or unknown for 45.5% of patients with hyperglycemic hyperosmolar syndrome. The leading cause of death in patients hospitalized for hyperglycemic hyperosmolar syndrome was acute myocardial infarction (18%), cardiac arrest of unknown cause (13%), and sepsis (9%).

Discussion

The present study showed that renal transplant recipients had a rate of diabetic ketoacidosis of 33.2/1000 person years in recipients a history of diabetes as a comorbid condition and 1.9/1000 person years in patients without a prior history of diabetes (measured as total hospitalizations for comparison with other reports). In

Table 3: Categorical variables of renal transplant recipients, 1 July 1994–30 June 1998[A]

Factor	Renal Transplant recipients	Missing, N (%)
N with valid Followup times		
Male Recipient (female)	23,827 (60.1)	0
African American (all other races)	9142 (23.1)	640 (1.5)
Graft loss[B] (Absent)	2815 (6.5%)	0
Cadaveric Donor (living donor)	27,369 (69.1)	0
Quartiles of Age (vs. >55 years)		
<33		
33–44		
45–55		
Diabetes as a comorbidity at listing (vs. absent)	7977 (24.7)	9931 (23.3)
History of Peritoneal Dialysis (vs. Hemodialysis)	8260 (19.6)	7855 (18.7)
Recipient HCV Positive (Yes/No)	2198 (5.6)	5743 (13.6)
Donor CMV Positive (Yes/No)	23,552 (57.1)	1620 (3.8)
Pretransplant dialysis (Yes/No)	31,046 (86)	284 (0.8)
Rejection (Yes/No)	8335 (19.8)	0
Cause of ESRD (vs. all others)		
Diabetes	7862 (19.7)	5178 (12.3%)
Hypertension	5495 (13.2)	5178 (12.3%)
Maintenance Medications		
Cyclosporine (vs. Tacrolimus)	31,448 (74.7)	3372 (8)
Tacrolimus (vs. Cyclosporine)	4623 (11.9)	3372 (8)
Mycophenolate (vs. Azathioprine)	18,608 (47.9)	3221 (7.6)
Azathioprine (vs. Mycophenolate)	16,308 (41.9)	3157 (7.5)
Prednisone (vs. all others)	34,451 (90.1)	3880 (9.2)
Induction Antibody Therapy	11,905 (28.3)	2277 (5.4)
Employment Status		
Working Full time	14,714	
Working Part time by choice	858	
Working Part time due to disease	2012	
Working part time reason unknown	200	
Not working	13,833	
Retired	2940	
Missing or unknown	7539	

Data given as the number (% of total) mean ± one standard deviation A = followup time truncated at three years post transplant ESRD = end-stage renal disease B = time-dependent variable

contrast, the estimated annual incidence of diabetic ketoacidosis in the general population was 4.6–8 episodes per 1000 diabetic subjects. [16] In the general population, the rate of diabetic ketoacidosis episodes as a primary hospitalization diagnosis was 0.3/1000 patients, and the rate of hyperglycemic hyperosmolar syndrome episodes was 0.04/1000 in 1997 (rates stratified for patients with diabetes were not available). [17] Although statistical comparison could not be performed due to the much higher rate of diabetes among renal transplant recipients than in the general population, the rates of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome in renal transplant recipients appear to be substantially higher than for either diabetic patients or for the general population, after excluding patients with combined kidney-pancreas transplants.

Certain risk factors were common to both the total risk of diabetic ketoacidosis and the risk of de novo diabetic ketoacidosis (diabetic ketoacidosis occurring in patients without a prior known history of diabetes). Consistent with the general population, African Americans were at higher risk of diabetic ketoacidosis than non-African Americans (Hispanic race was only introduced into the database recently). [18–21] The higher risk of African Americans was independent of other factors in the database, such as body mass index, graft loss, rejection episodes or employment status. Despite adjustment for these factors, socioeconomic factors could certainly not be excluded, and have been implicated in prior studies. Similarly, low body mass index was associated with diabetic ketoacidosis in either situation (in contrast to the association of high body mass with the increased risk of type II diabetes). [22] However, differences in gender and

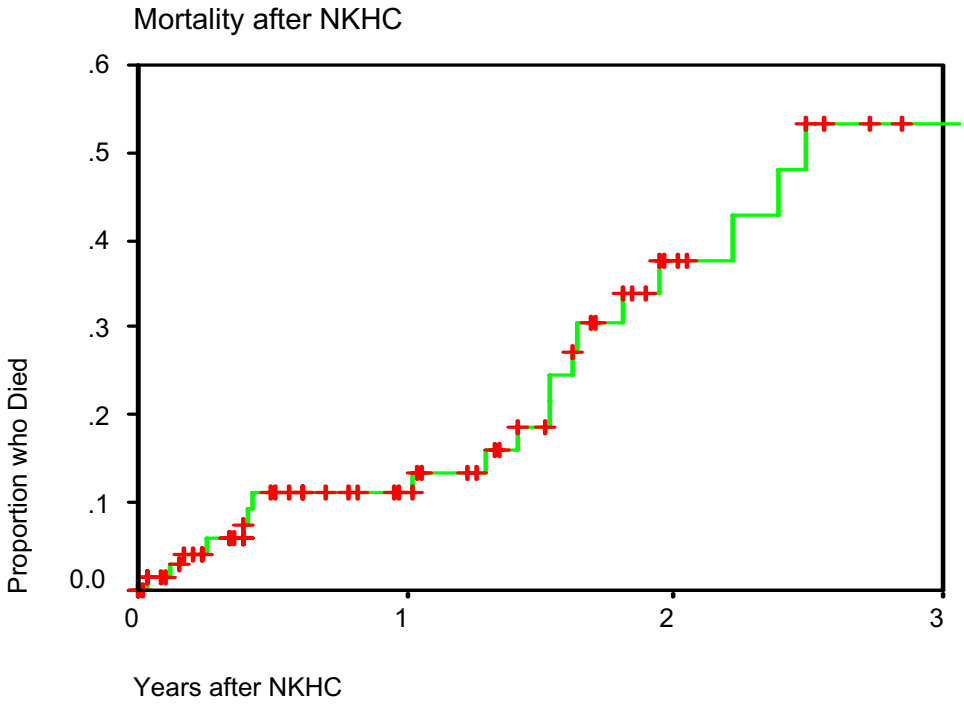

Figure 6
Mortality after hospitalization for hyperglycemic hyperosmolar syndrome. hyperglycemic hyperosmolar syndrome was associated with a significantly increased risk of mortality after renal transplantation (by Cox non-proportional hazards regression analysis, adjusted hazard ratio = 1.87, 95% CI, 1.22–2.88, $p < 0.004$). The risk of mortality after NKHC was roughly constant over time.

graft loss were not associated with de novo diabetic ketoacidosis. Each of these may reflect risk factors for diabetes in the general population. Conversely, donor type and use of maintenance tacrolimus were only associated with de novo diabetic ketoacidosis. The increased risk of cadaver donor type could be related to medication use. The relatively high rate of "de novo" diabetic ketoacidosis (diabetic ketoacidosis occurring in patients who did not have a known diagnosis of diabetes at the time of transplant) could represent drug-associated diabetic ketoacidosis, which has infrequently been reported with the use of both tacrolimus and cyclosporine. [3] Previous case series did not have sufficient sample size to determine competing risks between calcineurin inhibitors, but the present study would suggest the risk is greater with tacrolimus. Because of rapid changes in the use of tacrolimus during the study period, as indicated above, conclusions should be limited. We would certainly caution any interpretation of tacrolimus use since there were substantial temporal trends during the study, and tacrolimus was not approved by the FDA for use in kidney transplantation until 1997. As indicated, in our analysis limited to that time span, tacrolimus was not significantly associated with increased risk of diabetic ketoacidosis.

Almost all reports of post-transplant diabetes mellitus in the medical literature have either concerned type II diabetes or have not specified by type. Therefore, reported risk factors such as obesity, cumulative prednisone use, and hepatitis C status would not be expected to affect the risk of diabetic ketoacidosis, consistent with reports in the general population. This is in contrast to hyperglycemic hyperosmolar syndrome, which would be expected to occur disproportionately in patients with type II diabetes. While older age and higher BMI were significant in univariate analysis, they were not significant in multivariate analysis, while the significance of positive recipient hepatitis C serology persisted. Use of diabetes as an aggregate outcome, combining either both type I and type II diabetes, or combining diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome, might obscure the relationship with certain risk factors if the associations were in different directions (as is the case with body mass index, for example: low body mass index being associated with type I diabetes, and high body mass being associated with type II diabetes). Use of such aggregate outcomes might also have missed an association between hyperglycemic hyperosmolar syndrome and hepatitis C. The present study thus provides more indirect evidence that the post-transplant diabetes associated with hepatitis C infection is predominantly type II diabetes, as suggested in other reports. [23,24] This is in contrast to a lack of association between hepatitis C seropositivity and diabetes as a cause of renal failure, as we have previously reported. [25]

Nevertheless, the increasing rate of diabetic ketoacidosis noted during the study period (Figure 1, more marked for total diabetic ketoacidosis than de novo diabetic ketoacidosis) is in contrast to the decreasing rate of de novo diabetic ketoacidosis and stable rate of total diabetic ketoacidosis noted for users of tacrolimus (Figure 2). While this information is necessarily preliminary, it suggests the possibility that factors other than tacrolimus use may be responsible for the increasing rate of diabetic ketoacidosis noted during the study, which was independent of all other factors assessed. We did not find an association between diabetic ketoacidosis and viral infections other than hepatitis C, notably cytomegalovirus, nor did we find an association between diabetic ketoacidosis and antibody induction therapy, which would be expected to decrease immunity but might also allow for a greater propensity to viral infections. We can only point to another recent report by Bhalla et al, [26] which found that "de novo" post-transplant diabetes mellitus (confirmed by renal biopsy) was much more common and much more rapid in onset than previously suspected, and could not be explained by usual clinical predictors, which is quite similar to our findings. The authors implicated "novel mechanisms" as the reason for this rapid increase. Whether this represents a relationship with newly appreciated viral infections, such as polyomavirus, or other factors is presently unknown.

Both diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome were associated with an increased risk of mortality among renal transplant recipients, consistent with reports in the general population. [27,28] If anything, the relative risk associated with diabetic ketoacidosis was greater than that for hyperglycemic hyperosmolar syndrome, somewhat in contrast to the general population. However, previous population based reports have not adjusted for the difference in age of presentation for this differing conditions. Given the limitations of the database, causes of death were primarily cardiovascular and not infectious, also consistent with the general population. [16]

There are several limitations to this retrospective study. Findings are associative, not causative, and risk cannot be assigned without the ability to control for other variables prospectively during the course of the study. We could not assess the causes for hospitalization for diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, or how they were treated, including the use of insulin. This study could not independently verify the type of diabetes. We could not assess certain important risk factors, such as nutritional status, the use of alcohol or infection, with hospitalized diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome. However, ICD-9 coding for determining rates of medical conditions has been used in other published studies, [29] as well as the National Center for Health Statistics. http://www.cdc.gov/nchs The current study's limitation to hospitalized cases of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome would tend to underestimate the frequency of these conditions in this population. However, these conditions are almost universally managed by hospitalization in the United States. Another limitation of the study is the inability to track whether the patients were subsequently switched from tacrolimus or cyclosporine during the course of the present study. However, reports of conversion from cyclosporine to tacrolimus, [30,31] which are most commonly employed as a rescue agent for refractory acute or chronic rejection or cyclosporine toxicity, suggest that this number is very small. Similarly, conversion from tacrolimus to cyclosporine, most commonly due to tacrolimus induced diabetes, by published report appears to be even rarer. [32] The short followup duration of the study may also be a limitation. Strengths of the present analysis include its large size and population-based character, and relatively complete capture and followup.

In conclusion, rates of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome after renal transplantation

Table 4: Cox Regression Analysis

Factor						
N with valid Followup times	39,628		24,316		39,628	
	Time to diabetic ketoacidosis		**Time to de novo diabetic ketoacidosis[A]**		**Time to hyperglycemic hyperosmolar syndrome[B]**	
	P value	**Adjusted HR (95% CI)**	**P value**	**Adjusted HR (95% CI)**	**P value**	**Adjusted HR (95% CI)**
African American (all other races)	<0.0001	2.00 (1.63–2.48)	<0.0001	3.41 (1.99–5.84)		4.87 (3.18–7.45)
Graft loss[B] (Absent)	<0.0001	1.63 (1.25–2.12)				
Cadaveric Donor (living donor)			0.027	2.14 (1.09–4.19)		
Quartiles of Age (vs. >55 years)						
<33	<0.0001	6.64 (4.59–9.61)				
33–44	<0.0001	4.75 (3.31–6.79)		2.13 (1.34–3.37)		
45–55	<0.0001	2.16 (1.47–3.17)				
Diabetes at listing (vs. absent)		10.06 (7.60–13.30)	Excluded		0.0015	2.15 (1.34–3.46)
BMI <21.6 vs. >28.3 kg/m^2	<0.0001	1.94 (1.44–2.62)		2.33 (1.09–5.00)		
Recipient HCV Positive (Yes/No)					0.01	2.16 (1.20–3.89)
Year of Transplant	<0.0001	1.49 (1.33–1.67)		1.49 (1.25–1.78)	0.001	1.73 (1.17–2.56)
Pretransplant dialysis (Yes/No)	<0.0001	2.11 (1.42–3.12)				
Cause of ESRD (vs. all others)						
Diabetes	<0.0001	10.59 (8.52–13.18)	Excluded			
Maintenance Medications						
Tacrolimus (vs. Cyclosporine)			0.019	2.20 (1.13–4.24)		
Interaction Terms						
Tacrolimus*Cadaver Donor	0.02	2.27 (1.17–4.41)				
Tacrolimus*Year of Transplant			0.03	0.70 (0.50–0.97)		

Data given as the number (% of total) mean ± one standard deviation HR = hazard ratios, diabetic ketoacidosis = hospitalization for diabetic ketoacidosis, defined as ICD9 code 250.1x hyperglycemic hyperosmolar syndrome = hyperosmolar hyperglycemic syndrome (non-ketotic hyperosmolor coma), defined as ICD9 code 250.2x Due to the less frequent occurrence of hyperglycemic hyperosmolar syndrome, hyperglycemic hyperosmolar syndrome was not analyzed separately in patients without a prior history of diabetes mellitus (de novo hyperglycemic hyperosmolar syndrome). * = $p < 0.01$ vs. all other recipients by Chi Square Test vs. recipients without diabetic ketoacidosis A = followup time truncated at three years post transplant ESRD = end-stage renal disease B = time-dependent variable

were substantially higher than reported for the general population, whether in diabetic or non-diabetic populations. These rates appear to be increasing significantly over time, particularly for diabetic ketoacidosis, even as the risk for diabetic ketoacidosis in patients treated with tacrolimus is decreasing significantly. In addition, we identified high-risk groups for diabetic ketoacidosis, de novo diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome after renal transplantation, and confirmed the association of both diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome with increased mortality after renal transplantation.

Author contributions

KCA performed the primary analysis and wrote the first draft of the manuscript, and is the corresponding author.

VJB collaborated on the manuscript providing expertise on the primary subject matter

LYA supervised the manuscript and is a world expert on the USRDS database, as the Program Director for the USRDS

CMY developed the original concept for the manuscript and reviewed the final version.

Competing interests

None declared.

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