The Relationship Between Diabetes and Infectious Hospitalizations in Renal Transplant Recipients

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The implications of diabetes developing after kidney transplantation (PostTDM group) need further study. Worse graft survival is seen in PostTDM compared with nondiabetic (NonDM group) patients (1,2). Yet, there is paucity of data on the risk of infection, an issue that becomes even more important since posttransplant patients are already immunocompromised. Thus, we aim to compare the risk of infection in the posttransplant period in PostTDM patients and in patients who were diagnosed with diabetes before transplant (PreTDM group) with those without diabetes.

RESEARCH DESIGN AND METHODS

— Data were obtained from the U.S. Renal Data System (3). The study population was limited to adult renal transplant patients whose primary payer was Medicare to enable analysis of hospital outcomes. Primary (i.e., first time) kidney transplant recipients from the years 1995 to 2000 were included. Pancreas recipients were excluded.

The diagnosis of diabetes was obtained from Medicare claims using a previously validated method and from U.S. Renal Data System transplant files (2,4). Patients were classified as PreTDM if diabetes was detected before, or at the time of, hospitalization for transplantation. The remaining diabetic patients were classified as PostTDM.

The outcome of interest was infection requiring hospitalization (HI) and occurring in the posttransplant period. The survival time until development of HI was analyzed using Cox multivariate proportional hazard models. Graft loss was used as the censor. Since the onset of PostTDM was time dependent, and the label of NonDM could only be given if the patients did not develop diabetes during follow-up, PreTDM, PostTDM, and NonDM could not all be combined into a single model. Therefore, two models were constructed.

The first Cox model analyzed the hazard risk of HI between patients with and without PreTDM at the time of transplantation, corrected for possible confounders including recipients' age, sex, race, and BMI; HLA mismatch level; pretransplant dialysis time; donor type; induction treatments; immunosuppresion agents; donor and recipient cytomegalovirus test status at the time of transplant; gancyclovir use at the time of transplant; acute rejection; and delayed graft function. The second Cox model was constructed for PostTDM and NonDM, with PostTDM as a time-dependent variable. PreTDM was excluded from this model.

The costs of HI were estimated using actual Medicare payments for the inpatient claim on the date of the HI and were compared using Wilcoxon test. Infections were categorized into bacterial, viral, or fungal and frequencies compared by χ^2. The three most common kinds of bacterial infections were then compared in terms of frequencies.

RESULTS

— There were 29,966 recipients included. About 43% were NonDM, 42% had PreTDM, and 15% had PostTDM. Male subjects comprised 60% and 20% were aged >60 years.

The first Cox model showed a 43% increased hazard risk (95% CI 1.34–1.52) for developing HI in PreTDM compared with those who did not have PreTDM (i.e., NonDM plus PostTDM) at the time of transplantation. The second Cox model showed a 77% increased risk of HI in PostTDM patients compared with NonDM (1.59–1.96). The Cox analyses showed essentially the same results when death, instead of graft loss, was used as a censor.

Most infections were bacterial in nature ($P < 0.001$) (Table 1). Of these bacterial infections, septicemia tended to be the most common presentation, followed by pneumonia, urinary tract infection, and others ($P = 0.066$). The median cost of HI was $5,873 in NonDM transplant recipients, $6,110 in PreTDM, and $6,431 in PostTDM ($P < 0.01$).

CONCLUSIONS

— The health implications of PostTDM are being increasingly recognized, but its association with infections has not been delineated well. One small study (5) ($n = 181$) showed that a greater proportion of PreTDM and PostTDM patients had infections after transplantation compared with NonDM patients. However, infections in the PostTDM group in that study could have been analyzed at a time that those patients had not yet developed diabetes, so that risk could not be correctly inferred at the time of transplantation. We wanted to assess risk at the time of transplantation and also at the time that patients in the PostTDM group had already been diagnosed with diabetes. As such, the three patient groups could not be directly compared, but analysis nevertheless showed that PreTDM and PostTDM patients carry a higher risk than the reference group.

Compared with those whose primary payer was not Medicare, our study population had more patients that were aged ≥60 years and a slightly greater proportion of African Americans. However, race and age were included in our models as possible confounders, suggesting that our results may still be generalizable. Only hospitalized infections were counted to

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Abbreviations: HI, infection requiring hospitalization.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—*Infections according to causative organism*

	PreTDM group	PostTDM group	NonDM group	*P* value
Bacterial	1,822 (61)	619 (54.35)	941 (45.79)	<0.001
Viral	913 (30.57)	422 (37.05)	913 (44.43)	
Fungal	45 (1.51)	13 (1.14)	31 (1.51)	
Other	207 (6.93)	85 (7.46)	170 (8.27)	

Data are *n* (%).

limit the ascertainment bias, as infections occurring in the outpatient setting may not be recorded in billing claims, and the definition of infection can be variable. There is a possibility that not all HIs were documented, but these would probably be missed equally in all groups. Immunosuppressant dose and duration could not be analyzed from our dataset, and we feel this should be studied prospectively.

The ascertainment of diabetes is a limitation, since we had to rely on claims submissions; however, we chose a method that had previously been shown to be highly sensitive and specific (4).

In our study, the cost of HIs was higher in PreTDM and PostTDM than NonDM, consistent with a U.S. Medicare study showing that treatment of a renal transplant recipient who developed diabetes was ~$21,000 greater than that for a patient without diabetes by the end of 2 years posttransplantation (6). Our findings support that diabetes, whether newly diagnosed or long standing, is associated with worse clinical outcomes. Although international guidelines have been published to address detection and management of PostTDM, this condition is largely left unattended (7). Though our study does not prove causation, it nevertheless provides more impetus toward improving the management of patients with PreTDM and PostTDM alike.

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