Post-Transplant Diabetes Mellitus After Kidney Transplant in Hispanics and Caucasians Treated with Tacrolimus-Based Immunosuppression

Background: Development of post-transplant diabetes mellitus after kidney transplant (PTDM) significantly increases kidney graft loss and mortality. Several risk factors for PTDM have been reported, including Hispanic ethnicity and the use of calcineurin inhibitors and corticosteroids. The incidence and impact of PTDM in the Hispanic kidney transplant population is unknown.

Material/Methods: We retrospectively reviewed the medical records of 155 Hispanic and 124 Caucasian patients, who were not diabetics and underwent kidney transplant between January 2006 and December 2011. We analyzed their clinical outcomes at 12 months post-transplant, including the incidence of PTDM, acute rejection rates, and patient and graft survival.

Results: Hispanics who developed PTDM (n=22) were more than 10 years older and had higher body mass index (BMI) than Hispanics without PTDM (p<0.001 and p=0.001, respectively). Caucasians with PTDM (n=13) were non-significantly older (2.5 years) and had higher BMI than Caucasians without PTDM (p=0.526, p=0.043, respectively). The incidence of PTDM was not significantly different between Hispanics and Caucasians treated with tacrolimus-based immunosuppression (14.2% and 10.5%, respectively).

Conclusions: PTDM did not cause significant difference in short-term outcomes after kidney transplant in Hispanics or Caucasians. Larger multicenter prospective and long-term clinical trials are needed to validate these findings.

MeSH Keywords: Hispanic Americans • Kidney Transplantation • Tacrolimus

Abbreviations: ADA – American Diabetes Association; ESRD – end-stage renal disease; PRA – panel reactive antibody; OGGT – oral glucose tolerance test; PTDM – post-transplant diabetes mellitus; USRDS – United States Renal Data System; WHO – World Health Organization

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Background

Although short-term graft survival after kidney transplantation has dramatically improved over the last 20 years with the recent use of more effective immunosuppressive medications and better patient care, patients are experiencing serious drug-related complications that negatively impact long-term patient and graft survival [1]. Post-transplantation diabetes mellitus (PTDM) has also been a contributing factor.

It has been shown that PTDM significantly increases acute rejection, kidney graft loss, and mortality as well as healthcare costs [2,3]. Several risk factors for PTDM have been reported, including: older age [2,4], obesity[5], metabolic syndrome [6], family history of diabetes [7], prior history of glucose intolerance [8], African American or Hispanic race/ethnicity [9–12], cytomegalovirus infection [13,14], hepatitis C infection [15] and the use of calcineurin inhibitors [16,17] and corticosteroids [18–20]. It has been recognized that autosomal dominant polycystic kidney disease [21] and low serum magnesium levels pre- and post-transplant [22,23] are also risk factors for PTDM.

The incidence and impact of PTDM in the Hispanic kidney transplant population are not well defined. Eghtesad et al. studied the incidence of PTDM in Hispanics and Native Americans who received tacrolimus. He found that Hispanics had a lower incidence of PTDM compared to Native Americans (1/17 Hispanics and 4/14 Native Americans) [9]. Ciancio et al. found that Hispanics have a lower incidence of PTDM compared to African Americans under daclizumab induction therapy and tacrolimus, mycophenolate mofetil and prednisone (8.2% versus 10.8%) at 12 months post-transplant [10]. Gordon et al. analyzed the “Hispanic paradox” in transplantation (the phenomenon whereby Hispanics have comparable or even lower all-cause and infant mortality rates than those in non-Hispanic whites in the United States, despite typically ranking lower in socioeconomic indicators). She reported that the Hispanic paradox applies to the case of better transplant outcomes among Hispanics who undergo kidney transplant [24].

We retrospectively reviewed the medical records of Hispanic and Caucasian patients who did not have end-stage renal disease (ESRD) secondary to diabetes mellitus and underwent a first-time kidney transplant. We analyzed their clinical outcomes at 12 months post-transplant, including the incidence of PTDM, acute rejection rates, and patient and graft survival.

Material and Methods

A total of 486 first-time single kidney transplants were performed at our institution between January 1, 2006 and December 31, 2011. Patients older than 18 years, who were not known as diabetic pre-transplant, self-reported Hispanic or Caucasian who underwent first-time single kidney transplant and have a minimal follow-up of 12 months were included in this study. A total of 279 patients met the inclusion criteria. The medical records of 155 Hispanic and 124 Caucasian patients were retrospectively reviewed. All patients were divided into four groups: Hispanics with PTDM (n=22), Hispanics without PTDM (n=133), Caucasians with PTDM (n=13) and Caucasians without PTDM (n=111). Tacrolimus whole blood levels were about 8–10 ng/mL over the first 8 weeks, about 5–7 ng/mL at six months and about 5 ng/mL at 12 months post-transplant and thereafter. All patients received mycophenolate mofetil or mycophenolate sodium and prednisone. Prednisone dose was tapered down post-transplant, and by six months they were receiving 5 mg daily. Patients considered high risk for acute cellular rejection received induction therapy with anti-thymocyte globulin IV 1.5 mg/kg/dose for about 2–3 doses (total cumulative dose of 3–4.5 mg/kg). High risk patients were defined per our protocol as sensitized, calculated panel reactive antibody (PRA) greater than 20%, multiple pregnancies, African American race, ESRD due to autoimmune diseases, and cold ischemia time greater than 24 hours. On the other hand, patients considered low risk for acute rejection received basiliximab as an induction therapy.

We analyzed the incidence of PTDM, acute rejection, and patient and graft survival at 12 months post-transplant. PTDM was diagnosed according to the World Health Organization (WHO) and American Diabetes Association (ADA) diabetes guidelines [7]. Acute rejection was treated with methylprednisolone 500 mg IV bolus daily for three days. If the allograft function did not improve and kidney biopsy showed persistent acute cellular rejection without evidence of acute antibody mediated rejection, anti-thymocyte globulin therapy was initiated at 1.5 mg/kg/IV daily for 3–5 days. Antibody mediated rejection was treated with plasmapheresis and intravenous immunoglobulin with/without rituximab.

These analyses were performed using SPSS for Windows (version 23; IBM Corp., Armonk, NY, USA) and applying t-tests for continuous data and chi-square tests for categorical data. A p-values <0.05 were considered statistically significant. Graft and patient survivals were plotted utilizing the Kaplan-Meier method where a failure was the diagnosis of post-transplant diabetes mellitus.

This study was approved by the Institutional Review Board at Loma Linda University.

Results

Hispanics who developed PTDM were more than 10 years older and had higher BMI than Hispanics without PTDM (p<0.001 and
Caucasians with PTDM were non-significantly older (2.5 years) and had higher BMI than Caucasians without PTDM (p=0.526, p=0.043, respectively). One patient in the Hispanic group and none in the Caucasian group with PTDM had a history of hepatitis C viral infection. Three patients in the Hispanic group and one in the Caucasian group without PTDM had a history of hepatitis C viral infection. The number of patients who received deceased or living donor kidney transplants were not significantly different between Hispanics or Caucasians with and without PTDM (p=0.35, p=0.99, respectively) (Table 1). The incidence of PTDM in Hispanics was 14.2% and 10.5% in Caucasians 12 months post-transplant.

Serum creatinine levels at 12 months post-transplant were not significantly different between Hispanics or Caucasians with or without PTDM (p=0.16 and p=0.75, respectively). The 12-month acute rejection rate was not significantly different between Hispanics or Caucasians with or without PTDM (p=0.41 and p=0.55, respectively). No Hispanics or Caucasians with PTDM developed acute rejection (Table 2).

The 12-month graft survival for Hispanics with and without PTDM was 100% and 97.7% (p=0.63), respectively, and for Caucasians with and without PTDM was 100% and 98.2% (p=0.63), respectively. The 12-month patient survival for
Hispanics with and without PTDM was 100% and 98.5% (p=0.56), respectively and for Caucasians with and without PTDM was 100% for both (Table 2).

Figure 1 shows no significant differences between the Caucasians and Hispanics for graft survival (p=0.241 [Log Rank Mantel-Cox] and p=0.272 [Breslow Generalized Wilcoxon]). Figure 2 also shows no significant differences between Caucasians and Hispanics for patient survival (p=0.319 [Log Rank Mantel-Cox] and p=0.116 [Breslow Generalized Wilcoxon]).

Discussion

We found in this study that the incidence of PTDM was not significantly different between Hispanics and Caucasians treated with tacrolimus-based immunosuppression (14.2% and 10.5%, respectively). In addition, Hispanics and Caucasians both with and without PTDM had similar acute rejection rates and patient and graft survival 12 months post-transplant.

PTDM is a major complication after kidney transplantation. In 2003, an international consensus guidelines meeting defined the diagnostic criteria for PTDM, with approval from the WHO/ADA [7]. Since then, the diagnosis of PTDM became more uniform, making it easier to evaluate different risk factors and outcomes, but the cause of PTDM is still unknown.

The use of different diagnostic criteria used before 2003 contributed to the explanation regarding the great divergence of incidence of PTDM from 2% to 50% [11]. The one-year cumulative incidence of PTDM is lower, <10% in most studies, than it was 30 years ago [11]. Hjelmesaeth et al. reported that 20% of the kidney transplant recipients had PTDM 10 weeks after transplant [8]. Subsequently, Valderhaug et al. reported a significantly lower incidence of PTDM (13% versus 20%) and impaired glucose tolerance/impaired fasting glucose (18% versus 32%) at 10 weeks post-transplant with an oral glucose tolerance test (OGTT) comparing two different cohorts of kidney transplant patients, performed from 2004 to 2005 to patients performed from 1995 to 1996 [25]. They concluded that these findings were possibly due to more efficient immunosuppressive therapy, lower rejection rates and steroid doses [25].

PTDM has been shown to increase graft failure and mortality by 1.6- and 1.9-fold, respectively [2] and cardiovascular events by 1.7-fold [28]. Kuo et al. reported that the incidence of PTDM was lower than that reported by Kasiske et al. at 12 months post-transplant and no adverse impact of PTDM on transplant survival and cardiovascular mortality was found [29].

Recently, Wauters et al. reported that PTDM is a strong independent risk factor for major cardiovascular events and death, and this risk is independent of the presence of cardiovascular disease identified before transplantation [30]. Also, PTDM increases United States Medicare costs by $21,500 per patient by two years post-transplant [3].

Immunosuppression therapy is a major modifiable risk factor for the development of PTDM but the increasing risk of developing acute rejection has to be considered when selecting an immunosuppressive agent with less risk of developing PTDM.
The United States Multicenter Phase III Trial of tacrolimus therapy revealed about five times higher incidence of PTDM in kidney transplant patients receiving tacrolimus versus cyclosporine (19.9% versus 4%, respectively, p<0.0001). It also showed that tacrolimus was more effective than cyclosporine in preventing acute rejection in deceased donor kidney transplant recipients [31].

Vincenti et al. (the DIRECT study) showed the diabetogenicity of tacrolimus compared to cyclosporine (33.6% versus 26%, respectively, p=0.046) in a randomized control trial with no significant difference in short-term outcome [16]. No data about PTDM in Hispanics were reported in this study.

Cole et al. showed decreased kidney allograft survival after developing either acute rejection or PTDM, with the worst outcome if the patient developed both [32].

Due to the current lack of evidence, there is no specifically recommended immunosuppressive agent regarding the risk of developing PTDM alone. It is important to choose the most appropriate immunosuppressive therapy according to the patient’s immunologic risk of developing acute rejection [33].

Hispanic ethnicity is considered a significant risk factor for the development of PTDM but unfortunately, few publications have addressed this issue [2,34,35]. Eghtesad et al. reported that PTDM was significantly less of a problem in Hispanics, but a significant problem in Native Americans, especially in children [9]. Kasiske et al. reported that Hispanics who underwent kidney transplant had higher risk of PTDM (the relative risk (RR) was 1.35 [95% confidence interval (CI): 1.19–1.54]) but slightly reduced risk of graft failure (RR=0.77 [95% CI: 0.66–0.91]) compared to non-Hispanics/unknown group [2]. Pham et al. reported, using data from the United States Renal Data System (USRDS), that PTDM was more prevalent in African Americans (RR=1.68, p<0.0001) and Hispanics (RR=1.35, p<0.0001) compared with Caucasians [35]. Walczak et al. found that in Hispanics who have a family history of diabetes and undergo kidney transplant under tacrolimus-based immunosuppressive therapy, early steroid discontinuation did not decrease the incidence of PTDM. On the other hand, early steroid discontinuation eliminated the risk of PTDM in African Americans and Caucasians. These data suggested that tacrolimus is likely responsible for the high rate of PTDM in the Hispanic population.

In contrast to the previous studies, we found that the incidence of PTDM was not significantly different between Hispanics and Caucasians treated with tacrolimus-based immunosuppression and low dose prednisone maintenance therapy, 5 mg orally per day after six months post-transplant. In addition, there was no difference between patient and graft survival between Hispanics or Caucasians with and without PTDM.

Our study has several weaknesses that are important to emphasize. The studied sample was small, and as a result, type II error was more likely to occur. The diagnosis of PTDM was made based on fasting plasma glucose serum levels according to the 2003 international consensus guidelines [7]. OGTT was not used routinely in this study. The 12 months follow-up of this study does not allow for evaluation of the long-term consequences of diabetes in this population, specifically, the impact regarding patient and graft survival.

Conclusions

These data showed no significant differences in the incidence of PTDM, acute rejection rates, and patient and graft survival between Hispanic and Caucasian patients treated with tacrolimus-based immunosuppression at 12 months post-transplant. Larger multicenter prospective and long-term clinical trials are needed to validate these findings.

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