Kidney Medicine

Posttransplant Diabetes Mellitus and Immunosuppression Selection in Older and Obese Kidney Recipients

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Rationale & Objective: Posttransplant diabetes mellitus (DM) after kidney transplantation increases morbidity and mortality, particularly in older and obese recipients. We aimed to examine the impact of immunosuppression selection on the risk of posttransplant DM among both older and obese kidney transplant recipients.

Study Design: Retrospective database study.

Setting & Participants: Kidney-only transplant recipients aged ≥18 years from 2005 to 2016 in the United States from US Renal Data System records, which integrate Organ Procurement and Transplantation Network/United Network for Organ Sharing records with Medicare billing claims.

Exposures: Various immunosuppression regimens in the first 3 months after transplant.

Outcomes: Development of DM >3 months-to-1 year posttransplant.

Analytical Approach: We used multivariable Cox regression to compare the incidence of posttransplant DM by immunosuppression regimen with the reference regimen of thymoglobulin (TMG) or alemtuzumab (ALEM) with tacrolimus + mycophenolic acid + prednisone using inverse propensity weighting.

Results: 12.7% of kidney transplant recipients developed posttransplant DM with higher incidences in older (≥55 years vs <55 years: 16.7% vs 10.1%) and obese (body mass index [BMI] ≥ 30 kg/m^2 vs BMI < 30 kg/m^2: 17.1% vs 10.9%) patients. The incidence of posttransplant DM was lower with steroid avoidance [TMG/ALEM + no prednisone (8.4%) and IL2rAb + no prednisone (9.7%)] than TMG/ALEM with triple therapy (13.1%). After adjustment for donor and recipient characteristics, TMG/ALEM with steroid avoidance was beneficial for all groups [age < 55 years: adjusted HR (aHR), 0.63 (95% confidence interval [CI], 0.54-0.72); age ≥ 55 years: aHR, 0.69 (95% CI, 0.60-0.79); BMI < 30 kg/m^2: aHR, 0.69 (95% CI, 0.60-0.78); BMI ≥ 30 kg/m^2: aHR, 0.67 (95% CI, 0.57-0.79)]. However, IL2rAb with steroid avoidance was beneficial only for older patients (aHR, 0.76; 95% CI, 0.58-0.99) and for those with BMI < 30 kg/m^2 (aHR, 0.63; 95% CI, 0.46-0.87).

Limitations: Retrospective study and lacked data on immunosuppression levels.

Conclusions: The beneficial impact of steroid avoidance using tacrolimus on posttransplant DM appears to differ by patient age and induction regimen.

Visual Abstract included

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Posttransplant diabetes mellitus (DM) is a serious and common complication following solid organ transplant, generally occurring within the first 2-3 years after transplant.[1-6] Despite efforts to prevent posttransplant DM, it occurs in as many as 10%-20% of nondiabetic kidney transplant recipients and is associated with premature cardiovascular disease, graft loss, and mortality.[2,7-17] Previous studies have identified risk factors for posttransplant DM, including obesity, metabolic syndrome, cytomegalovirus infection, hepatitis C viremia, and calcineurin inhibitor (CNI) therapy, especially tacrolimus.[14,18-26] In addition, older age is a strong and consistent risk factor for posttransplant DM among kidney transplant recipients and has been associated with greater posttransplant morbidity.[1,8,14,18,27-29] The median age at the time of kidney transplant has consistently increased worldwide, driven by population aging and increasing acceptance of older (aged ≥55 years) kidney transplant candidates for waitlisting and transplant.[30-34] Kidney transplant recipients have been shown to have a 1.5-fold higher risk per decade of age of developing posttransplant DM.[18,35]

Immunosuppression selection has been identified as a potentially modifiable risk factor for developing posttransplant DM.[36] Although tacrolimus and sirolimus have been associated with increased risks of posttransplant DM, data on steroid avoidance/withdrawal as a strategy to decrease posttransplant DM risk are conflicting.[22-26,37-43] Because the use of regimens that reduced the risk of posttransplant DM [cyclosporine (CsA)-based regimens or steroid avoidance] have historically been associated with an increasing risk of rejection, recommendations published in 2014 following an international consensus meeting on posttransplant DM suggested that the immunosuppression regimens should fully optimize patient and allograft survival without concern for enhancing the risk of posttransplant DM.[5,44] Similar recommendations were issued by the British Clinical Diabetologists and Renal Association and American Diabetes Association in 2021.[5,44,45] These guidelines drew on data mainly from the CsA era, often without effective induction therapy.[22-26,37-43] In contrast, transplantation guidelines now recommend that tacrolimus and mycophenolate mofetil be used as first-line maintenance immunosuppression agents with appropriate induction

PLAIN-LANGUAGE SUMMARY

Posttransplant diabetes mellitus (DM) increases morbidity and mortality after kidney transplantation, particularly in older and obese recipients. Given that immunosuppression selection is a potentially modifiable risk factor for posttransplant DM, we assessed associations of immunosuppression regimen with posttransplant DM among older and obese recipients using a linkage of national transplant registry and Medicare claims data. We observed benefits of corticosteroid-sparing regimens with appropriate induction therapy on posttransplant DM risk among patients aged ≥55 years or those with a body mass index of ≥30 kg/m^2, after adjusting for other demographic and clinical characteristics. These findings support the consideration of the risk of nonimmune complications along with rejection risk when selecting immunosuppression regimens in kidney transplant recipients to minimize immunosuppression-associated complications.

medications, mitigating the risk of rejection associated with steroid avoidance.[46,47]

Previous studies evaluating the risk of posttransplant DM have not assessed the benefits of alternative immunosuppression strategies, such as steroid avoidance/withdrawal, to reduce the risk of posttransplant DM among older and obese recipients, who are more at risk of metabolic complications.[41-43] Older kidney transplant recipients tend to have a lower acute rejection risk due to immunosenescence reducing the risk of rejection and, potentially, the need for long-term triple therapy.[48,49] Recent evidence from our team suggests that lower-intensity immunosuppression regimens (eg, steroid-sparing regimens) appear beneficial in older kidney transplant recipients, reducing posttransplant death and graft loss.[50] Similarly, obese patients have more than a 2-fold increase in the incidence of posttransplant DM compared with nonobese patients; however, they have an increased risk of rejection.[18] In this study, we examined the impact of immunosuppression selection on the development of posttransplant DM in a contemporary national sample of kidney transplant recipients. We specifically considered the risk of posttransplant DM among both older and obese kidney transplant recipients using a linkage of national clinical registry data and Medicare billing claims.

METHODS

Data Source and Sampling

Study data were drawn from US Renal Data System records, which integrate Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing records with Medicare billing claims. The study identified kidney-only transplant recipients aged ≥18 years from 2005 to 2016 in the United States. Younger and older adults were defined as ages 18-54 years and ≥55 years, respectively. Patients were selected for inclusion if they had Medicare as the primary payer at the time of transplant and had Medicare-reimbursed prescriptions and fills for immunosuppressive medications in the first 3 months after transplant. We excluded patients with documentation of diabetes in the OPTN transplant candidate or recipient registration forms. The cohort included patients with Medicare primary insurance and without pretransplant diabetes (based on OPTN registration information or Medicare claims for diabetes within 1 year before transplant). This study was deemed to be human subjects exempt by the Saint Louis University Institutional Review Board.

Definition of Immunosuppression Regimens

We determined the use of induction agents based on center-reported data from the OPTN. We determined the early immunosuppression regimen based on Medicare pharmacy claims for immunosuppression agents submitted within the first 3 months after transplant and reimbursed through Part B or Part D benefits. We categorized patients based on induction and maintenance immunosuppression regimens into 7 study regimens, as follows:

(1) Triple maintenance (tacrolimus + mycophenolic acid/azathioprine + prednisone), after T-cell–depleting induction: antithymocyte globulin (TMG) or alemtuzumab (ALEM) (reference)
(2) Triple maintenance after IL-2 receptor antibody (IL2rAb): IL2rAb + triple therapy
(3) Steroid avoidance/withdrawal after T-cell–depleting induction: TMG/ALEM + no prednisone
(4) Steroid avoidance after IL-2rAb induction: IL2rAb + no prednisone
(5) Antimetabolite avoidance: tacrolimus alone or tacrolimus + prednisone with any induction
(6) Mammalian target of rapamycin inhibitor (mTORi)–based regimens
(7) CsA-based regimens

Outcome Measures

The outcome of interest was posttransplant DM >3 months-to-1 year after transplant. We ascertained the diagnosis of DM from Medicare claims using *International Classification of Diseases, Ninth Revision, Clinical Modification* (through September 2015) and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (starting October 2015) diagnosis codes on billing claims (codes 250.x and E08-E13, respectively) that occurred or persisted beyond 3 months after transplant.

Statistical Analysis

Clinical characteristics of the study sample were described as proportions. We grouped continuous variables into clinically relevant categories. We classified the missing data in the registry as "not reported" and included this

indicator in the regression analyses, as per previous methods.[51-55] For each variable, the proportion of data that was not reported is summarized in Table S1. We compared distributions of clinical characteristics according to the immunosuppression regimen using the $\chi 2$ test.

We modeled the association between immunosuppression selection and the development of posttransplant DM using a Cox proportional hazard frailty model, allowing for clustering by transplant center and permitting the correlation between failures within the same transplant center, with origin time for models at 3 months after transplant (after the period of immunosuppression classification). The DM incidence >3 months-to-1 year posttrasplant associated with each immunosuppression regimen was compared with the reference regimen of TMG/ALEM + triple therapy. We adjusted the model for potentially confounding differences in the distribution of clinical characteristics using inverse probability of treatment weighting, as per previous methods.[56,57] The inverse probability of treatment weighting uses propensity weights to create analytic samples that are more similar and allow a better estimation of the independent impact of immunosuppression selection on the development of posttransplant DM. To construct the weights, we modeled the probability of developing posttransplant DM, comparing each immunosuppression regimen with the reference regimen (TMG/ALEM + triple therapy), given the patient's age, sex, race, number of human leukocyte antigen mismatches, panel reactive antibody, hepatitis C virus status, donor age, donor type (living or deceased), expanded criteria donor, and donation after cardiac death. Weights were stabilized; a robust sandwich estimator was used to prevent the underestimation of the variance. Good balance was achieved on all confounders (standardized absolute mean difference: <0.2 for all covariates and <0.1 overall for all models). Patients with death or graft failure were censored at the time of these events. All other patients were followed to the first posttransplant anniversary or loss of Medicare coverage. Given the known association of recipient body mass index (BMI) and age with the development of diabetes, we performed a prespecified subgroup analysis based on age (<55 years vs ≥55 years) and obesity (BMI < 30 kg/m^2 vs BMI ≥ 30 kg/m^2) and investigated the potential interaction of immunosuppression with age and obesity on the risk of posttransplant DM. A P value of <0.05 was considered statistically significant. The data management and analysis were performed using SAS version 9.4 (SAS institute Inc).

RESULTS

Clinical Characteristics

Among 193,984 kidney transplant recipients in the study period, 40,108 had Medicare insurance at transplant and did not have pretransplant diabetes. Compared with the general transplant population, the study sample of Medicare beneficences without diabetes differed in age, race, employment status, BMI, and cause of end-stage kidney disease (Table S1), consistent with prior reports**.** Among the sample, 38.0% recipients were ≥55 years old, 58.8% were men, 30.2% were African American, and 27.5% had a BMI of ≥30 kg/m^2. TMG/ALEM + triple therapy was the most common immunosuppression regimen (47.2%), followed by TMG/ALEM + no prednisone (20.0%), IL2rAb + triple therapy (16.0%), CsA-based regimens (5.6%), and mTORi-based regimens (5.7%). IL2rAb + no prednisone (2.2%) and tacrolimus or tacrolimus + prednisone with any induction (3.3%) were not commonly used. The distribution of clinical characteristics of kidney transplant recipients varied among immunosuppression regimens (Table 1).

Incidence and Risk of Posttransplant DM Among different Immunosuppression Regimens: Older Versus Younger

The incidence of DM >3 months-to-1 year posttransplant was significantly higher among older adults in the sample (age ≥55 years, 16.7% vs <55 years, 10.1%; $P < 0.001$). Among older patients, the incidence of posttransplant DM within 12 months varied more than 2.3-fold across regimens, from 11.6% among patients on TMG/ALEM + no prednisone to 26.3% among patients on mTORi-based regimens (Fig 1A**)**. Among younger patients, the incidence of posttransplant DM varied from 6.1% (IL2rAb + no prednisone) to 20.2% (mTORi).

After adjusting for potential confounding differences due to clinical characteristics, the risks of posttransplant DM remained significantly different across regimens (Fig 2A). Among older recipients, the risk of posttransplant DM was decreased in those treated with TMG/ALEM + no prednisone [adjusted hazard ratio (aHR), 0.69; 95% CI, 0.60-0.79] or with IL2rAb + no prednisone (aHR, 0.76; 95% CI, 0.58-0.99), whereas the risks were higher with mTORi-based therapy and CsA-based regimens than with TMG/ALEM + triple therapy. The impact of mTORi immunosuppression on the risk of posttransplant DM varied by age [age ≥ 55 years: aHR, 1.69 (95% CI, 1.46-1.96); age < 55 years: aHR, 1.24 (95% CI, 1.03-1.49); interaction by age $P = 0.002$]. Among younger patients, only TMG/ALEM + no prednisone was associated with a lower risk of posttransplant DM (aHR, 0.63; 95% CI, 0.54-0.72). There was no statistically significant benefit to IL2rAb + no prednisone regimen in younger patients.

Effect of Obesity on Risks of Posttransplant DM Among Different Immunosuppression Regimens

Obese patients had significantly greater risks of posttransplant DM, regardless of the immunosuppression regimen (BMI < 30 kg/m^2: 10.9%, BMI ≥ 30 kg/m^2: 17.1%; $P < 0.0001$). Obese patients treated with mTORi-based regimens had the highest incidence of DM >3 months-to-1 year posttransplant (32.4%), whereas nonobese patients

Table 1. Distributions Early Immunosuppression Regimen Use According to Baseline Kidney Transplant Recipient Traits, Donor Type, and Transplant Factors

	TMG/ALEM + Triple Therapy (Reference), n (%)	IL2rAb + Triple Therapy, n (%)	TMG/ALEM + No Pred, n (%)	IL2rAb + No Pred, n (%)	Tac, Tac + Pred, n (%)	mTORi-based, n (%)	CsA-based, n (%)
Age (y)	—	[a]	[a]	[a]	[b]	[b]	[a]
<55	12,606 (66.5)	3,544 (55.1)	4,801 (59.7)	354 (40.7)	823 (62.8)	1,461(64.0)	1,271 (56.9)
≥55	6,304 (33.5)	2,884 (44.9)	3,238 (40.3)	516 (59.3)	487 (37.2)	822 (36.0)	961 (43.1)
Sex	—	[a]	[a]	[b]	[b]	[a]	[a]
Male	10,527 (55.6)	4,063 (63.2)	4,930 (61.3)	541 (62.2)	785 (59.9)	1,395 (61.1)	1,341 (60.1)
Female	8,419 (44.4)	2,365 (36.8)	3,109 (38.7)	329 (37.8)	525 (40.1)	888 (38.9)	891 (39.9)
Race	—	[a]	[a]	[a]	[a]	[a]	[a]
White	8,130 (42.9)	3,428 (53.3)	3,983 (49.6)	532 (61.2)	691 (52.8)	1,259 (55.2)	1,199 (53.7)
African American	6,705 (35.4)	1,512 (23.5)	2,279 (28.4)	153 (17.6)	356 (27.2)	617 (27.0)	501 (22.5)
Hispanic	3,091 (16.3)	1,012 (15.7)	1,322 (16.4)	126 (14.5)	202 (15.4)	292 (12.8)	315 (14.1)
Other[c]	1,020 (5.4)	476 (7.4)	455 (5.7)	59 (6.8)	61 (4.7)	115 (5.0)	217 (9.7)
Employment status	—	—	[a]	[b]	[a]	[b]	[a]
Working	3,858 (20.4)	1,295 (20.2)	1,866 (23.2)	193 (22.2)	347 (26.5)	425 (18.6)	389 (17.4)
Not working	13,427 (70.9)	4,629 (72.0)	5,418 (67.4)	627 (72.1)	829 (63.3)	1,692 (74.1)	1,545 (69.2)
Not reported	1,661 (8.8)	504 (7.8)	755 (9.4)	50 (5.8)	134 (10.2)	166 (7.3)	298 (13.4)
Body mass index, kg/m^2							
<30	13,296 (70.2)	4,792 (74.6)[a]	5,467 (68.0)[b]	676 (77.7)[a]	918 (70.1)	1,674 (73.3)[b]	1,557 (69.8)
≥30	5,426 (28.6)	1,587 (24.7)[a]	2,307 (28.7)	185 (21.3)[a]	347 (26.5)	578 (25.3)[b]	625 (28.0)
Not reported	224 (1.2)	49 (0.8)[b]	265 (3.3)[a]	9 (1.0)	45 (3.4)[a]	31 (1.4)	50 (2.2)[a]
Comorbid conditions							
Hypertension	7,383 (39.0)	2,620 (40.8)[b]	3,403 (42.3)[a]	374 (43.0)[b]	536 (40.9)	996 (43.6)[a]	930 (41.7)[b]
CAD	441 (2.3)	191 (3.0)[b]	201 (2.5)	32 (3.7)[b]	41 (3.1)	81 (3.6)[b]	76 (3.4)[b]
CVD	68 (0.4)	31 (0.5)	42 (0.5)	2 (0.2)	5 (0.4)	20 (0.9)[b]	11 (0.5)
PVD	692 (3.7)	260 (4.0)	284 (3.5)	36 (4.1)	25 (1.9)[b]	77 (3.4)	90 (4.0)
COPD	42 (0.2)	24 (0.4)[b]	29 (0.4)[b]	6 (0.7)	2 (0.2)	12 (0.5)[b]	16 (0.7)[a]
Hepatitis C positive	909 (4.8)	328 (5.1)	289 (3.6)[a]	57 (6.6)[b]	62 (4.7)	92 (4.0)	184 (8.2)[a]
EBV positive	14,169 (74.8)	4,980 (77.5)[a]	5,866 (73.0)[b]	614 (70.6)[b]	925 (70.6)[b]	1,703 (74.6)	1,400 (62.7)[a]
Cause of ESKD	—	[a]	[a]	[a]	[b]	[b]	[a]
Hypertension	6,115 (32.3)	2,006 (31.2)	2,749 (34.2)	273 (31.4)	396 (30.2)	778 (34.1)	672 (30.1)
Glomerulonephritis	8,496 (44.8)	2,694 (44.9)	3,309 (41.2)	334 (38.4)	549 (41.9)	930 (40.7)	950 (43.6)
PKD	1,902 (10.0)	737 (11.5)	992 (12.3)	103 (11.8)	156 (11.9)	278 (12.2)	250 (11.2)
Other	2,433 (12.8)	991 (15.4)	989 (12.3)	160 (18.4)	209 (16.0)	297 (13.0)	360 (16.1)
Duration of dialysis, mo	—	[a]	[a]	[a]	[a]	[a]	[a]
None (preemptive)	710 (3.8)	580 (9.0)	528 (6.6)	118 (13.6)	104 (7.9)	123 (5.4)	181 (8.1)
>0-24	2,506 (13.2)	1,396 (21.7)	1,421 (17.7)	237 (27.2)	266 (20.3)	421 (18.4)	459 (20.6)
25-60	6,023 (31.8)	2,209 (34.4)	3,027 (37.7)	285 (32.8)	461 (35.2)	837 (36.7)	697 (31.2)
>60	9,704 (51.2)	2,240 (34.9)	3,058 (38.0)	229 (26.3)	478 (36.5)	902 (39.5)	889 (39.8)
Not reported	3 (0.0)	3 (0.1)	5 (0.13)	1 (0.1)	1 (0.1)	0 (0.0)	6 (0.3)
Most current PRA level, %	—	[a]	[a]	[a]	[a]	[a]	[a]
<10	10,815 (57.1)	5,086 (79.1)	6,109 (76.0)	709 (81.5)	919 (70.2)	1,569 (68.7)	1,599 (71.6)
10-79	4,186 (22.1)	854 (13.3)	1,185 (14.7)	104 (12.0)	218 (16.6)	392 (17.2)	364 (16.3)
≥80	3,624 (19.1)	290 (4.5)	558 (6.9)	22 (2.5)	126 (9.6)	188 (8.2)	183 (8.2)
Not reported	321 (1.7)	198 (3.1)	187 (2.3)	35 (4.0)	47 (3.6)	134 (5.9)	86 (3.9)
HLA mismatches	—	[b]	—	[a]	—	[b]	[a]
Zero A, B, DR	1,151 (6.1)	471 (7.3)	461 (5.7)	123 (14.1)	87 (6.6)	174 (7.6)	194 (8.7)
Zero DR	2,141 (11.3)	681 (10.6)	918 (11.4)	92 (10.6)	144 (11.0)	240 (10.5)	248 (11.1)
Other	15,654 (82.6)	5,276 (82.1)	6,660 (82.6)	655 (75.3)	1,079 (82.4)	1,869 (81.9)	1,790 (80.2)

(Continued)

Table 1 (Cont'd). Distributions Early Immunosuppression Regimen Use According to Baseline Kidney Transplant Recipient Traits, Donor Type, and Transplant Factors

	TMG/ALEM + Triple Therapy (Reference), n (%)	IL2rAb + Triple Therapy, n (%)	TMG/ALEM + No Pred, n (%)	IL2rAb + No Pred, n (%)	Tac, Tac + Pred, n (%)	mTORi-based, n (%)	CsA-based, n (%)
Cold ischemia time, h	—	[a]	[a]	[a]	[a]	[a]	[a]
≤12	7,346 (38.8)	3,156 (49.1)	3,177 (39.5)	440 (50.6)	546 (41.7)	1,051 (46.0)	887 (39.7)
13-24	7,922 (41.8)	2,296 (35.7)	2,883 (35.9)	254 (29.2)	499 (38.1)	820 (35.9)	830 (37.2)
25-36	2,373 (12.5)	560 (8.7)	1,032 (12.8)	60 (6.9)	136 (10.4)	238 (10.4)	250 (11.2)
≥37	539 (2.8)	81 (1.3)	434 (5.4)	10 (1.2)	32 (2.4)	62 (2.7)	48 (2.2)
Not reported	766 (4.0)	335 (5.2)	513 (6.4)	106 (12.2)	97 (7.4)	112 (4.9)	217 (9.7)
Previous transplant	—	[a]	[a]	[a]	[a]	[a]	[a]
Yes	4,449 (23.5)	633 (9.9)	846 (10.5)	77 (8.9)	232 (17.7)	407 (17.8)	390 (17.5)
No	14,497 (76.5)	5,795 (90.2)	7,193 (89.5)	793 (91.2)	1,078 (82.3)	1,876 (82.2)	1,842 (82.5)
Donor type	—	[a]	[a]	[a]	[a]	[a]	[a]
Living donor	3,481 (18.4)	1,987 (30.9)	2,100 (26.1)	366 (42.1)	335 (25.6)	571 (20.0)	592 (26.5)
Deceased, KPDI <20	3,427 (18.1)	1,127 (17.5)	1,300 (16.2)	122 (14.0)	257 (19.6)	340 (14.9)	407 (18.2)
Deceased, KDPI 20-85	10,815 (57.1)	2,937 (45.7)	4,046 (50.3)	312 (35.9)	618 (47.2)	1,191 (52.2)	1,098 (49.2)
Deceased, KDPI >85	1,223 (6.5)	377 (5.9)	593 (7.4)	70 (8.1)	100 (7.6)	181 (7.9)	135 (6.1)
Transplant era	—	[a]	[a]	[a]	[a]	[a]	—
2005-2008	3,759 (19.8)	1,644 (25.6)	2,031 (25.3)	307 (35.3)	554 (42.3)	962 (42.1)	1,071 (48.0)
2009-2012	7,274 (38.4)	2,541 (39.5)	3,242 (40.3)	361 (41.5)	459 (35.0)	759 (33.3)	807 (36.2)
2013-2016	7,913 (41.8)	2,243 (34.9)	2,766 (34.4)	202 (23.2)	297 (22.7)	562 (24.6)	354 (15.9)

Note: Data presented as N (column percentages %). Triple therapy was composed of Tac + mycophenolic acid/azathioprine + Pred.
Abbreviations: ALEM, Alemtuzumab; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CsA, cyclosporine A; CVD, cerebral vascular disease; EBV, Epstein-Barr virus; ESKD, end-stage kidney disease; HLA, human leukocyte antigen; IL2rAb, interleukin-2 receptor antibody; KDPI, kidney donor profile index; mTORi, mammalian target of rapamycin inhibitor; PKD, polycystic kidney disease; PRA, panel reactive antibody; Pred, prednisone use documented post-transplant; PVD, peripheral vascular disease; Tac, tacrolimus; TMG, thymoglobulin.
[a]$P < 0.0001$.
[b]$P < 0.05$ to 0.0002.
[c]"Other" race includes Asian, American Indian, Pacific Islander, and multiracial.

on tacrolimus or tacrolimus+ prednisone had the lowest (7.1%; Fig 1B). The use of TMG/ALEM + no prednisone reduced the risk of posttransplant DM in patients with a BMI ≥ 30 kg/m^2 to 11.5%, whereas 16.0% of patients on IL2rAb + no prednisone developed posttransplant DM.

After adjustment for confounding, steroid avoidance with TMG/ALEM induction reduced the risk of posttransplant DM in obese patients (aHR, 0.67; 95% CI, 0.57-0.76; Fig 2B). Conversely, steroid avoidance with IL2rAb induction resulted in a risk of posttransplant DM equivalent to that of obese patients managed with triple therapy (aHR, 0.99; 95% CI, 0.66-1.49). The risk of posttransplant DM with mTORi-based therapy was significantly greater than that of triple therapy (aHR, 1.40; 95% CI, 1.12-1.75). Among nonobese patients, both steroid avoidance regimens were associated with lower rates of posttransplant DM [TMG/ALEM + no prednisone: aHR, 0.69 (95% CI, 0.60-0.78); IL2rAb: aHR, 0.63 (95% CI, 0.46-0.87)], whereas mTORi use increased the risk (aHR, 1.22; 95% CI, 1.04-1.44).

DISCUSSION

This study of a large, contemporary sample of kidney transplant patients confirms an overall benefit of corticosteroid-sparing regimens among patients at risk of posttransplant DM, including patients who are older or who have higher BMI, after adjusting for comorbid conditions (eg, hepatitis C) and patient characteristics (eg, race/ethnicity). Although current published recommendations suggest that immunosuppression regimens should be chosen to provide the "best immunologic outcomes" for patients, irrespective of the posttransplant DM risk, this recommendation does not account for differences in kidney transplant recipients' risks and benefits.[5,44] Previous studies that evaluated the risks of posttransplant DM among kidney transplant recipients with various immunosuppression regimens have not been updated with current tacrolimus-based maintenance therapy and effective induction.

Older patients (age ≥ 55 years) are at a increased risk of posttransplant DM and appear to be optimally managed with a steroid-free regimen when accompanied by appropriate induction (either TMG/ALEM or IL-2rAb). Older transplant patient populations are at greater risk of noninfectious complications and are less likely to have a rejection after transplant as a result of immunosenescence.[22-26,37,39-43,50] Recent data from a transplant registry analysis has suggested potential patient and graft

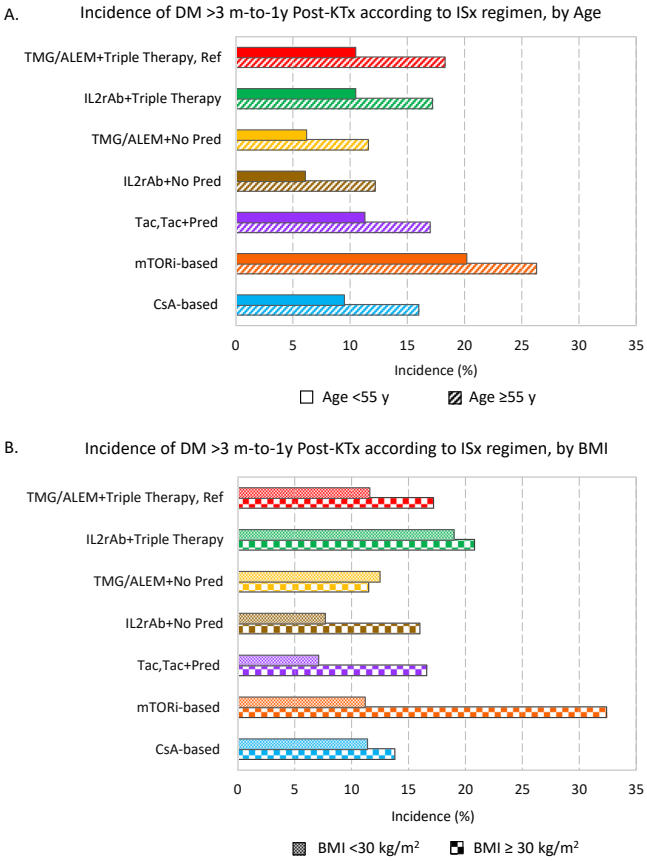

Figure 1. Differential incidences of DM >3 months-to-1 year after transplant among kidney transplant patients according to immunosuppression regimen based on (A) age at transplant and (B) BMI at transplant. Triple Therapy was composed of Tac + MPA/AZA + Pred. Abbreviations: ALEM, alemtuzumab; AZA, azathioprine; BMI, body mass index; CsA, cyclosporine A; DM, diabetes mellitus; IL2rAb, interleukin-2 receptor antibody; ISx, immunosuppression; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; Pred, prednisone; Tac, tacrolimus; TMG, thymoglobulin.

survival benefits of lower-intensity immunosuppression regimens (eg, steroid-sparing regimens) for older kidney transplant recipients.[50] Conversely, younger and obese patients derive a benefit from steroid avoidance regimens, but only if the offsetting risk of rejection is mitigated by T-cell–depleting therapy (TMG/ALEM).

There are conflicting data on the long-term benefits of steroid withdrawal compared with long-term, low-dose corticosteroid treatment on the risk of posttransplant DM.[41,42] Although the withdrawal of 10 mg of prednisone daily has been associated with lower insulin resistance, there is less certainty about the benefit of its elimination in kidney transplant recipients receiving lower doses of prednisone, such as 5 mg daily.[58,59] A prior report has suggested that insulin sensitivity improved by tapering the dose of prednisone from 10 mg/day to 5 mg/day, but there was no additional improvement when withdrawing from a 5-mg dose.[59] Clinical data on the benefit of steroid avoidance protocols have evolved as maintenance regimens have shifted from CsA to tacrolimus. In the HARMONY trial comparing induction regimens in patients who all received tacrolimus + mycophenolic acid, rapid corticosteroid withdrawal was linked to a lower incidence of posttransplant DM without increasing the risk of rejection.[60] There are limited data in previous studies on the effects of steroid avoidance/withdrawal among older and obese recipients.[41,42,61-64] A recent Scientific Registry of Transplant Recipients (SRTR) study of 44,635 first kidney transplant recipients with BMI ≥ 30 kg/m^2 also showed that recipients with prednisone-free maintenance immunosuppression had significantly better outcomes, including patient and graft survival, compared with recipients on maintenance immunosuppression with prednisone.[65] In this study, the continuation of any prednisone regimen was associated with higher rates of posttransplant DM in both low- and high-risk patients.

CNIs are well recognized as increasing the risk of hyperglycemia, as they impair insulin sensitivity, decrease insulin release, and directly damage pancreatic islet cells.[22-26,66] Therefore, the minimization or avoidance of CNI as a strategy to decrease the risk of posttransplant DM has been evaluated.[67] The DIRECT randomized controlled trial confirmed the heightened diabetogenicity of tacrolimus when compared to CsA among recipients of a kidney transplant.[68,69] However, this trial used tacrolimus trough levels that were much higher than those used in current practice. Diabetes reversal after replacing tacrolimus with CsA in kidney transplant patients with posttransplant DM has been reported.[70] Thus, conversion from tacrolimus to CsA to improve the metabolism of glucose in transplant recipients has been proposed.[71] However, tacrolimus is superior in preventing acute rejection, and increased rejection episodes following conversion from tacrolimus to CsA have been reported, likely leading to the resumption of chronic steroid therapy.[40,72] The current study did not confirm a reduction in the risk of posttransplant DM in de novo CsA-based regimens compared with tacrolimus-based regimens with steroid avoidance. It is possible that the diabetogenic effect of tacrolimus is dose dependent and the tacrolimus trough levels that were used in clinical practice in older recipients were not as high as those younger recipients, thus explaining why a comparable risk of posttransplant DM was seen when compared to CsA-based regimens in this population.[73] Alternatively, the infrequent use of CsA may limit statistical power in this subgroup analysis. Furthermore, the diabetogenic effects of tacrolimus are likely exacerbated by the concomitant use of steroids. Thus, compared with tacrolimus and CsA in triple therapy regimens, there was no significant benefit for either CNI. In the absence of steroids, tacrolimus' superior protection against rejection may decrease the incidence of posttransplant DM by limiting the use of high-dose steroids for rejection. It is important to note that given the relatively uncommon use of CsA nationally, the CsA regimen in our study included both steroid-sparing and triple therapy patients. However, given the high

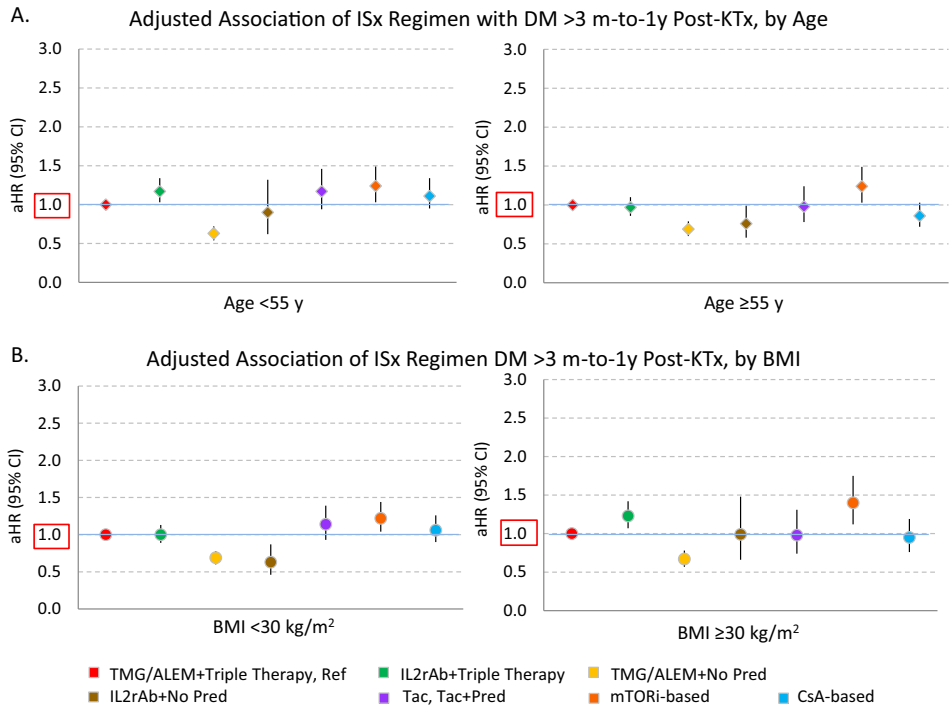

Figure 2. Adjusted risks of DM >3 months-to-1 year after transplant among patients treated with different immunosuppression regimens based on (A) age at transplant and (B) BMI at transplant. Triple Therapy was composed of Tac + mycophenolic acid/azathioprine + Pred. Abbreviations: aHR, adjusted hazard ratio; ALEM, alemtuzumab; BMI, body mass index; CsA, cyclosporine A; CI, confidence interval; DM, diabetes mellitus; IL2rAb, interleukin-2 receptor antibody; ISx, immunosuppression; mTORi, mammalian target of rapamycin inhibitor; Pred, prednisone; Tac, tacrolimus; TMG, thymoglobulin.

rates of rejection in CsA patients without prednisone, routine prednisone sparing is unlikely to be used frequently; thus, the inclusion of aggregated CsA patients is appropriate.

The use of de novo mTORi-based regimens has generally been shown to be inferior to tacrolimus maintenance, given the increased risk of rejection. Prior examinations of the US Renal Data System data have also demonstrated that sirolimus use is associated with an increased risk of posttransplant DM, likely due to the impact of long-term prednisone use in this population.[39] The incidence of posttransplant DM was higher with sirolimus (either combined with mycophenolate mofetil or CNIs) than with CNI and mycophenolate mofetil alone.[39] Conversely, in the Symphony study, which used lower target levels of sirolimus (3 and 7 ng/mL), mTORi recipients developed posttransplant DM at an incidence rate between those of patients on CsA and tacrolimus.[40] In addition, both a reduction in sensitivity to insulin and a weakened compensatory insulin response remain when recipients are converted from either CsA or tacrolimus to sirolimus, suggesting that the use of mTORi regimens alone is not enough to reverse the glycometabolics of transplant recipients.[74] Among kidney transplant patients, our study also established that an mTORi-based regimen did not provide benefits against posttransplant DM risk. Given that retrospective studies identify associations of mTORi-based regimens with an increased risk of mortality, particularly in older kidney transplant recipients, use of these regimens to avoid tacrolimus does not appear to be beneficial.[50,75]

This registry-based study has limitations. First, based on the nature of the database, data on immunosuppression levels, including trough levels of CNIs and/or mTORi, and other laboratory data were not available. Data suggest that the effects of tacrolimus on the risk of posttransplant DM are dose dependent and are pronounced in recipients with a history of hypertriglyceridemia and insulin resistance.[73,76] Second, the choice of immunosuppression regimen might have been affected by uncaptured risk factors in the database, such as prior rejection episodes; donor characteristics; intolerance of standard medications, including hematologic abnormalities; a history of malignancy; or the inability to afford these medications. Recipients at a high risk of posttransplant DM may have been switched to CsA preemptively, artificially increasing the risk of posttransplant DM in this group. Lastly, the incidence of posttransplant DM in our study was 12.7% over the first year, which is somewhat lower than in prior reports based on clinical records reviews.[7-9] The oral glucose tolerance test is the preferred test to diagnose posttransplant DM, but results of this test are not available in Medicare claims or OPTN data.[44] It is possible that posttransplant DM was underreported when ascertained from Medicare diagnosis codes, but there is no reason to

believe that underreporting differs by immunosuppression regimen. Consequently, the inferences presented in this article should be valid and are grounded in study of one of the largest samples of older transplant recipients examined for this outcome to date.

In summary, among Medicare-insured kidney transplant recipients, steroid-free immunosuppression is associated with a lower risk of posttransplant DM. This benefit was confirmed for high-risk patients (older adults; BMI ≥ 30 kg/m^2); however, the importance of concomitant cell depleting differed. These data support the consideration of the risk of nonimmune complications along with the rejection risk when selecting immunosuppression regimens in kidney transplant recipients, to minimize patient morbidity from immunosuppression-associated side effects.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Characteristics of Medicare-insured patients in the study sample compared to kidney transplant recipients not included in the cohort.

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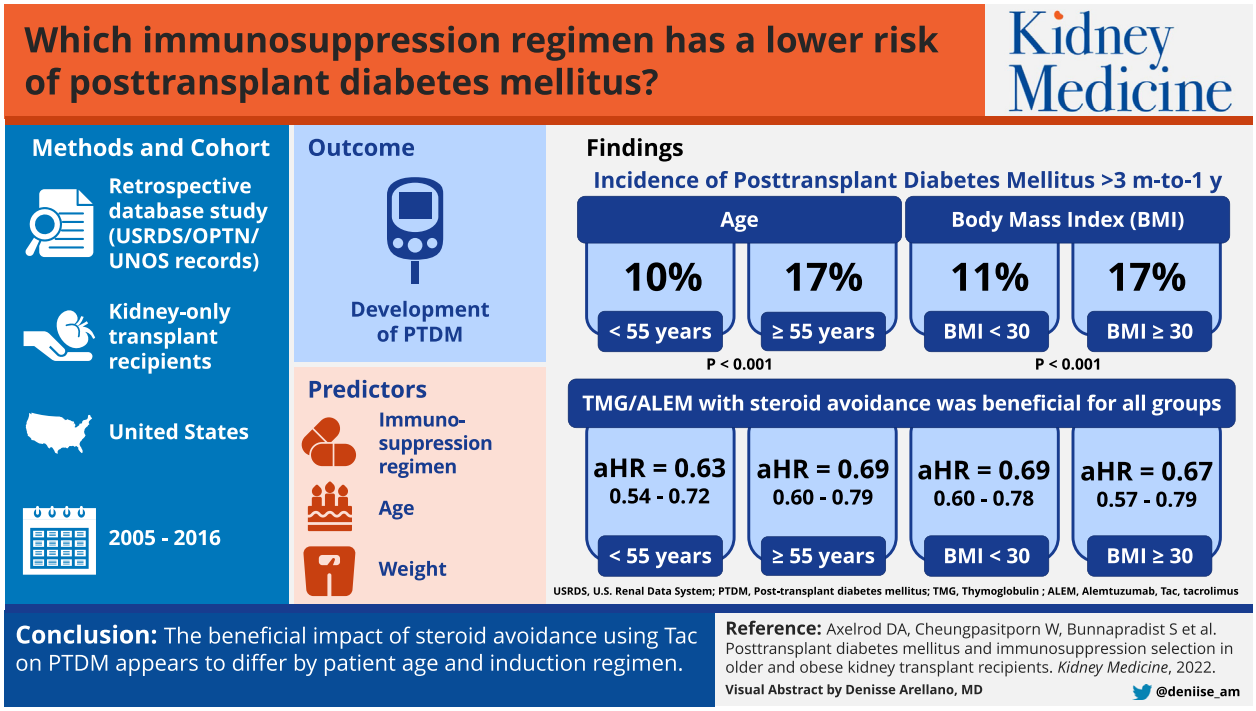
Which immunosuppression regimen has a lower risk of posttransplant diabetes mellitus?
Kidney Medicine
Methods and Cohort
Retrospective database study (USRDS/OPTN/ UNOS records)
Kidney-only transplant recipients
United States
2005 - 2016
Outcome
Development of PTDM
Predictors
Immuno-suppression regimen
Age
Weight
Findings
Incidence of Posttransplant Diabetes Mellitus >3 m-to-1 y
Age
Body Mass Index (BMI)
10%
< 55 years
17%
≥ 55 years
11%
BMI < 30
17%
BMI ≥ 30
P < 0.001
P < 0.001
TMG/ALEM with steroid avoidance was beneficial for all groups
aHR = 0.63
0.54 - 0.72
< 55 years
aHR = 0.69
0.60 - 0.79
≥ 55 years
aHR = 0.69
0.60 - 0.78
BMI < 30
aHR = 0.67
0.57 - 0.79
BMI ≥ 30
USRDS, U.S. Renal Data System; PTDM, Post-transplant diabetes mellitus; TMG, Thymoglobulin ; ALEM, Alemtuzumab, Tac, tacrolimus
Conclusion: The beneficial impact of steroid avoidance using Tac on PTDM appears to differ by patient age and induction regimen.
Reference: Axelrod DA, Cheungpasitporn W, Bunnapradist S et al. Posttransplant diabetes mellitus and immunosuppression selection in older and obese kidney transplant recipients. Kidney Medicine, 2022.
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