Dubai Diabetes and Endocrinology Journal

Research Article

Dubai Diabetes Endocrinol J
DOI: 10.1159/000531665

Received: March 15, 2023
Accepted: June 14, 2023
Published online: August 4, 2023

Post-Transplant Diabetes Mellitus in Renal Transplant Recipients, Single-Centre Data: Incidence, Risk Factors, and Effect on Graft Function and Mortality

Dileep Kumar[a] Kashif Gulzar[a] Fakhriya J. Alalawi[a] Ayman Aly Seddik[b] Hind Alnour[a] Maseer Ahmad[a] Sima Najad[a] Hussain Yousif[c] Mohammad Hussain Railey[a] Amna Khalifa Alhadari[a]

[a]Department of Nephrology, Dubai Hospital, Dubai Health Authority, Dubai, UAE; [b]Department of Nephrology, AIN Shams University, Cairo, Egypt; [c]Department of Nephrology, Shaikh Khalifa Medical City, Ajman, UAE

Keywords
Transplant · Post-transplant diabetes mellitus · Immunosuppressant · Prednisolone · Cyclosporine · Cytomegalovirus · Hepatitis C virus

Abstract

Background: De novo post-transplant diabetes mellitus (PTDM) is a frequent complication among renal transplant recipients; it confers a high risk for graft failure and patient mortality. This single-centre study aimed to determine the incidence and risk factors of PTDM and its effects on graft outcome and mortality. ***Methods:*** In a single-centre longitudinal cohort analysis of 383 non-diabetic renal transplant follow-up recipients, outcomes were analysed through a detailed chart review. We hypothesized that different donor and recipient characters such as age, gender, and HLA mismatch would affect PTDM development in renal transplant recipients. PTDM is defined on basis of fasting plasma sugar (≥7 mmol/L or ≥126 mg/dL), random plasma sugar (≥11.1 mmol/L or ≥200 mg/dL), and glycated haemoglobin (HBA1C: >6.5% or 48 mmol/mol). We assessed PTDM incidence, risk factors, and its effect on patient mortality and graft outcome using Cox regression. ***Results:*** The mean age at the time of transplantation was 35.70 (±14.27) years, and 50.91% were male. PTDM incidence in the study period was 23.30%. Independent risk factors include older age at the time of transplantation, cyclosporine immunosuppression, cytomegalovirus, and hepatitis C virus infection. PTDM is not associated with graft dysfunction, whereas it significantly carries high mortality. ***Conclusion:*** PTDM is common among renal transplant recipients. Older age at the time of transplantation, cyclosporine immunosuppression, cytomegalovirus, and hepatitis C virus are risk factors. PTDM carries high mortality but is not associated with graft failure.

Introduction

Hundreds of thousands of patients' lives have been changed with solid organ transplantation worldwide since the first renal transplant was done in 1954 between identical twins. Challenges like infection and graft rejection are dealt with advancements in immunosuppressive

karger@karger.com
www.karger.com/dde

Correspondence to:
Kashif Gulzar, kashifsmcian@gmail.com

medications and antimicrobials [1]. Importantly, nevertheless, cardiovascular disease is associated with higher morbidity and mortality in renal transplant recipients, and de novo post-transplant diabetes mellitus (PTDM) is considered a significant contributor to this adverse outcome. Diagnostic criteria for PTDM are based on fasting plasma sugar (≥7 mmol/L or ≥126 mg/dL), random plasma sugar (≥11.1 mmol/L or ≥200 mg/dL), and glycated haemoglobin (HBA1C: >6.5% or 48 mmol/mol) (Table 1) [2–4]; however, HBA1C in early post-operative period in renal disease patients can be affected by iron deficiency, blood loss, or blood transfusion; therefore, for PTDM screening, HBA1C should merely be used after 3 months of transplantation [5]. Early hyperglycaemia after surgery is quite common, and it may or may not be associated with long-term hyperglycaemia (PTDM). Common causes of this hyperglycaemia are stress, infection, pain, initial high dosage of immunosuppressive medications, and feeding (enteral and parenteral) [6]. PTDM affects 10–40% of renal transplant recipients [7]; it also confers a higher risk of graft failure and mortality as compared to those recipients who do not suffer from PTDM [8]. The central idea of this study is to report the incidence and risk factors of PTDM among our population in Dubai and its effect on graft function and mortality in renal transplant recipients (Table 1).

Material and Methods

We conducted a retrospective observational study to identify the incidences and risk factors of PTDM and its effect on graft survival in renal transplant recipients, who attended Dubai Hospital renal transplant clinic from January 1, 1990, to December 31, 2020. Mean follow-up period was 11.7 ± 3.3 years. Patients gave their consent to use their data for research by signing the general consent available in the medical record system. PTDM was diagnosed based on clinical presentation, plasma glucose (fasting and random), and HBA1C. Patients with ages less than 14 years were excluded from this study.

Data Collection

Medical records of the study population were reviewed using patients' manual medical files and electronic medical records (Epic Hyperspace, year 2019) to retrieve patients' demographic characteristics, follow-up visit notes, hospital admission records, and laboratory findings. Demographic characteristics include age, sex, and comorbidities. Laboratory data consist of plasma glucose (fasting and random), HBA1C, renal functions, urine studies (urine routine, urine protein-creatinine ratio), and serum albumin. Normal ranges of these parameters were provided by the laboratory. Diagnostic criteria for PTDM are based on any of the following: persistent fasting plasma sugar (≥7 mmol/L or ≥126 mg/dL), random plasma sugar (≥11.1 mmol/L or ≥200 mg/dL) with symptoms, and HBA1C (>6.5% or 48 mmol/mol) were solely used to diagnose PTDM after 1 year (Table 1). Plasma glucose readings, renal functions, urine studies on follow-up visits, and HBA1C readings for three months were monitored. Graft dysfunction is defined as a 15% increase in creatinine from baseline [9]. Primary outcome of study was to report incidence of PTDM, whereas secondary outcome was to determine effect of PTDM on renal graft survival and mortality in renal transplant recipients.

Statistical Analysis

Continuous variables are described as mean ± standard deviation and median with interquartile range values for normally distributed and non-normally distributed data, respectively. Categorical variables were presented as frequency and percentage. Independent *t* test and Mann-Whitney test were used for normally distributed and non-normally distributed continuous variables, respectively, and categorical data were compared with help of Pearson's χ^2 test or Fischer's exact test. The correlation between risk factors and PTDM was analysed by Cox regression, where PTDM was considered a time-dependent variable because this complication started at different times following the transplant. A p value of <0.05 was considered statistically significant. SPSS version 20 was used for statistical analysis.

Results

Baseline Characteristics

We could retrieve data of a total of 512 renal transplant recipients followed up in our transplant clinic during the study period (January 1991 to December 2021). PTDM patients' demographic characteristics, graft survival, and mortality rate were compared with those of non-diabetic renal transplant recipients so patients known to have diabetes mellitus before renal transplantation were excluded (n = 129). Basic patients' characteristics are shown in Table 2. During the mean follow-up period of 11.7 ± 3.3 years, out of 383 patients, 118 (n = 23.30%) renal transplant recipients suffered from PTDM. Overall mean age at the time of transplantation was 35.70 (±14.27) years, and more than half of study population was male (50.91%). PTDM patients belonged to relatively higher age group than non-diabetics (40.48 vs. 34 years, p = <0.05), also there were more females than males (23.72% vs. 63.01%, p = <0.05). Chronic glomerulonephritis (38.13 vs. 36.22), hypertension (12.71 vs. 15.09), and obstructive uropathy (6.77 vs. 8.97) were common causes of renal failure in PTDM and non-diabetic renal transplant recipients. Generally, 72.89% and 24.93% (n = 269 and 92) organ donors were predominantly live unrelated and related, respectively, whereas cadaver organ donors were 2.16% (n = 8) only. In the PTDM group as compared to non-diabetics, organ donors were more among live unrelated (PTDM vs. non-diabetics: 77.96% vs. 70.51%, p = 0.16). Prednisolone (93.21%, n = 357) is the most

Table 1. Diagnostic criteria of PTDM

1. Fasting glucose >126 mg/dL (7 mmol/L) on more than one occasion
2. Random glucose >200 mg/dL (11.1 mmol/L) with symptoms
3. Two-hour glucose after a 75-g OGTT of >200 mg/dL (11.1 mmol/L)
4. HbA1c >6.5%

commonly used immunosuppressive medication in our study population, followed by mycophenolate mofetil (MMF) (60.31%, n = 231), cyclosporine (57.44%, n = 222), tacrolimus (31.59%, n = 121), azathioprine (21.14%, n = 81), and sirolimus (10.96%, n = 42), also 84.85% (n = 325) renal transplant recipients were using triple immunosuppression, and cyclosporine, MMF, and prednisolone were the most common combination used (28.45%, n = 109). In the PTDM group as compared to non-diabetic renal transplant recipients, prednisolone (PTDM vs. non-diabetics: 96.61% vs. 91.69%, p = 0.07), cyclosporine (PTDM vs. non-diabetics: 66.94% vs. 53.20%, p = 0.01), and sirolimus (PTDM vs. non-diabetics: 15.25% vs. 9.05%, p = 0.07) were used more, and only cyclosporine is statistically associated with PTDM. Whereas MMF (PTDM vs. non-diabetics: 56.77% vs. 61.88%, p = 0.34), tacrolimus (PTDM vs. non-Diabetics: 27.96% vs. 33.20%, p = 0.30), azathioprine (PTDM vs. non-diabetics: 20.33% vs. 21.50%, p = 0.79) were used more by non-diabetics relatively. 92.37% (n = 109) of PTDM population was on triple immunosuppressive medications compared to 81.57% (n = 216, p = 0.007) of non-diabetics, and cyclosporine, MMF, and prednisolone were the most common combinations used in both groups (PTDM vs. non-diabetics: 29.66% vs. 27.54%). The overall median creatinine for our transplant population was 1.2 mg/dL (0.5–1.7), also 19.84 (n = 76) people lost their graft and reached chronic kidney disease stage 5. As compared to PTDM, renal functions were relatively well preserved (PTDM vs. non-diabetics: 1.58 ± 0.99 vs. 0.7 ± 0.89, p = 0.517) in non-diabetics; also lesser number of patients (PTDM vs. non-diabetics: 22.80% vs. 19.53%, p = 0.322) lost their graft and reached chronic kidney disease stage 5.

Viral Infection

Post-transplant CMV infection as evident with positive PCR (PTDM vs. non-diabetics: 31.91% vs. 12.30%, p = 0.003) as well as hepatitis C virus infection (HCV) (PTDM vs. non-diabetics: 22.88% vs. 9.43%, p = 0.003) rate was significantly higher among PTDM patients, while hepatitis B virus infection rate was 4.76% (n = 6) in PTDM and 2.26% (n = 6) in non-diabetic renal transplant recipients.

Risk Factors for PTDM

Univariate regression analysis was used to determine factors that independently predicted the development of PTDM (Table 3). The proven significant factors were inserted into multivariate model, as shown in Table 4. Older age of recipient (overall and also at the time of renal transplantation), male gender, cyclosporine immunosuppression, and post-transplant cytomegalovirus and HCV are the factors that independently predict development of PTDM in renal transplant recipients.

Graft Survival and Patient Mortality

Overall renal graft survival at 1, 5, and 10 years was 97.39%, 85.64%, and 75.93%, respectively. There was no difference in graft survival between PTDM and non-diabetic statistically. At 5 and 10 years, graft survival were 88.13% and 72.03% for PTDM patients and 84.52% and 69.52% for non-diabetes. A total of 59 (15.40%) renal transplant recipients expired in study period. The mortality in the PTDM group was significantly higher (PTDM vs. non-diabetic: 22.03 vs. 12.45%, p = 0.016) than in the non-diabetic group. Overall and in PTDM population, common cause of death was infection (47.45% and 57.69%, respectively), whereas cardiac-related causes were more prevalent in non-diabetics (n = 17, 51.51%).

Discussion

In this single-centre study, we found an incidence of PTDM of 23.04% (n = 118) in renal transplant recipients. PTDM incidence in renal transplant recipients varies between 10 and 40%, and this variation depends on the length of follow-up, type of immunosuppressive, and diagnostic criteria [10]. Malik et al. [11] reported 29 and 20.55% PTDM incidence in 5 years and 6 months after transplantation, respectively [11, 12]. In studies using OGTT for diagnosis, Hjelmesaeth et al. [13] observed an incidence of PTDM at 18% in 1995, which has reduced to 11% in 2012 [14]. PTDM pathophysiology is multifactorial; risk factors for its development are pre-and post-transplantation, also allograft-associated. Increased age of recipient (>40 years), obesity (BMI >30 kg/m^2), family history of diabetes, and high-risk ethnicities (Asian and African-American) are known pre-transplant risk factors [15, 16]. We also found age at transplantation in the PTDM group was higher than that of non-diabetics (40.48 vs. 34 years, p = <0.05). Medical comorbidities in renal transplant recipients: HCV, cystic fibrosis, and polycystic kidney disease can also influence the development of PTDM [17, 18]. Studies have shown significantly reduced insulin sensitivity in HCV-positive renal

Table 2. Patients' characteristics

Patients' characteristics	Renal transplant recipients, *n* = 383	PTDM, *n* = 118, 23.30%	Non-PTDM, *n* = 265, 76.70%	*p* value
Age, years, mean (±SD)	49.51 (±14.85)	54.79 (±12.48)	47.22 (±15.23)	<0.05
Age at transplantation, years, mean (±SD)	35.70 (±14.27)	40.48 (±12.59)	34 (±14.48)	<0.05
Sex (male)	195 (50.91)	28 (23.72)	167 (63.01)	<0.05
Primary disease, *n* (%)				
Chronic glomerulonephritis	141 (36.81)	45 (38.13)	96 (36.22)	
Hypertension	55 (14.36)	15 (12.71)	40 (15.09)	
Chronic allograft nephropathy	14 (3.65)	8 (6.77)	6 (2.26)	
Obstructive uropathy	31 (8.09)	8 (6.77)	23 (8.97)	
IgA nephropathy	18 (4.69)	5 (4.23)	13 (4.90)	
ADPKD	26 (6.78)	8 (6.77)	18 (6.79)	
Systemic lupus nephritis	15 (3.91)	4 (3.38)	11 (4.15)	
FSGS	16 (4.17)	4 (3.38)	12 (4.52)	
Analgesic nephropathy	5 (1.30)	4 (3.38)	1 (0.37)	
MPGN	12 (3.13)	4 (3.38)	8 (3.01)	
Solitary kidney	14 (3.65)	8 (6.77)	6 (2.26)	
Chronic pyelonephritis	12 (3.13)	3 (2.54)	9 (3.39)	
TIN	2 (0.52)	1 (0.84)	1 (0.37)	
HUS	1 (0.26)	1 (0.84)	0 (0.00)	
Alport syndrome	6 (1.56)	0	6 (2.26)	
Hypoplastic kidneys	9 (2.34)	0	9 (3.39)	
Comorbid, *n* (%)				
Hypertension	124 (32.37)	59 (50)	65 (24.52)	
IHD	7 (1.87)	4 (3.38)	3 (1.13)	
Chronic hepatitis	35 (9.13)	4 (3.38)	31 (11.69)	
Dyslipidaemia	110 (28.72)	3 (2.54)	107 (40.37)	
Peptic ulcer disease	3 (0.78)	2 (1.69)	1 (0.37)	
CHF	88 (22.97)	2 (1.69)	86 (32.45)	
Asthma	5 (1.30)	2 (1.69)	3 (1.13)	
Rheumatoid arthritis	10 (2.61)	1 (0.84)	9 (3.39)	
Donor, *n* (%)	*n* = 369	*N* = 118	*n* = 251	0.168
LURD	269 (72.89)	92 (77.96)	177 (70.51)	
LRD	92 (24.93)	24 (20.33)	68 (27.09)	
Cadaver	8 (2.16)	2 (1.69)	6 (2.39)	
Immunosuppression, *n* (%)				0.795
Azathioprine	81 (21.14)	24 (20.33)	57 (21.50)	
Cyclosporine	220 (57.44)	79 (66.94)	141 (53.20)	<0.05
MMF	231 (60.31)	67 (56.77)	164 (61.88)	0.345
Prednisolone	357 (93.21)	114 (96.61)	243 (91.69)	0.077
Sirolimus	42 (10.96)	18 (15.25)	24 (9.05)	0.073
Tacrolimus	121 (31.59)	33 (27.96)	88 (33.20)	0.308
TWO	35 (9.13)	9 (7.62)	26 (9.81)	0.565
CO + PRED	15 (3.91)	7 (5.93)	8 (3.01)	
AZA + PRED	1 (0.26)	0 (0)	1 (0.37)	
AZA + CO	1 (0.26)	0 (0)	1 (0.37)	
AZA + SIRO	1 (0.26)	0 (0)	1 (0.37)	
AZA + TAC	1 (0.26)	0 (0)	1 (0.37)	
CO + MMF	2 (0.52)	0 (0)	2 (0.75)	
MMF + PRED	5 (1.30)	0 (0)	5 (1.88)	
MMF + TAC	2 (0.52)	0 (0)	2 (0.75)	
PRED + TAC	6 (1.56)	1 (0.84)	5 (1.88)	
PRED + SIRO	1 (0.26)	1 (0.84)	0 (0)	
Three	325 (84.85)	109 (92.37)	216 (81.50)	0.007
AZA + CO + PRE	70 (18.27)	26 (22.03)	46 (17.35)	
AZA + PRED + SIRO	1 (0.26)	0 (0)	1 (0.37)	
AZA + PRED + TAC	6 (1.56)	0 (0)	6 (2.26)	

Table 2 (continued)

Patients' characteristics	Renal transplant recipients, *n* = 383	PTDM, *n* = 118, 23.30%	Non-PTDM, *n* = 265, 76.70%	*p* value
CO + PRED + SIR	18 (4.69)	11 (9.35)	7 (2.64)	
CO + MMF + PRED	109 (28.45)	35 (29.66)	73 (27.54)	
CO + PRED + TAC	3 (0.78)	2 (1.69)	1 (0.37)	
EVO + MMF + PRED	2 (0.52)	0 (0)	2 (0.75)	
MMF + PRED + SIRO	14 (3.65)	3 (2.54)	11 (4.15)	
MMF + PRED + TAC	96 (25.06)	29 (24.57)	66 (24.90)	
PRED + TAC + SIRO	4 (1.04)	1 (0.84)	3 (1.13)	
PRED + SIRO + LEF	2 (0.52)	2 (1.69)	0 (0)	
Creatinine, mg/dL, median (IQR)	1.2 (0.5–1.7), *n* = 294	1.58 (±0.99), *n* = 88	0.7 (±0.89), *n* = 206	0.517
≤1.2	148 (50.34)	44 (38.56)	104 (40.62)	
1.3–2	97 (24.56)	28 (24.56)	69 (26.95)	
2.1–3	29 (9.86)	10 (8.77)	19 (7.42)	
3.1–4	11 (3.74)	2 (1.75)	9 (3.51)	
4.1–5	3 (1.02)	2 (1.75)	1 (0.37)	
>5.1	6 (2.04)	2 (1.75)	4 (1.56)	
Graft failure on dialysis	76 (19.84)	26 (6.78)	50 (13.05)	0.322
Proteinuria	0.5 (0.03–1.27), *n* = 334	0.218 (0.15–1), *n* = 107	0.6 (0.3–1.67), *n* = 227	0.307
≤500 mg/d	226 (67.66)	66 (61.68)	160 (70.48)	
500 mg^{-1} gm	51 (15.26)	17 (15.88)	34 (14.97)	
1–1.5 g	6 (1.79)	2 (1.87)	4 (1.76)	
1.5–2	6 (1.79)	2 (1.87)	4 (1.76)	
2.1–3	18 (5.38)	7 (6.54)	11 (4.84)	
3.1–5	14 (4.19)	7 (6.54)	7 (3.08)	
>5.1	13 (3.89)	6 (5.60)	7 (3.08)	
Post-transplant CMV infection	*n* = 307	*n* = 47	*n* = 260	<0.05
CMV-DNA −ve	260 (84.69)	32 (60.08)	228 (87.69)	
CMV-DNA +ve	47 (15.30)	15 (31.91)	32 (12.30)	
Post-transplant HCV infection				<0.05
Negative	331 (86.42)	91 (73.12)	240 (90.57)	
Positive	52 (13.57)	27 (22.88)	25 (9.43)	
Post-transplant HBV infection				0.868
Negative	*371 (96.86)*	112 (95.23)	259 (97.73)	
Positive	*12 (3.13)*	6 (4.76)	6 (2.26)	
Acute rejection episodes	*n* = 352	*n* = 112	*n* = 240	0.961
No	252 (71.59)	81 (72.32)	171 (71.25)	
Yes	100 (28.40)	31 (5.35)	69 (28.75)	
Graft survival, years, mean (±SD)	11.92 (±6.87)	12.85 (±6.68)	11.32 (±6.95)	0.059
Less than 1 years	5 (1.69)	1 (0.86)	4 (2.23)	
1.1–5	52 (17.62)	14 (12.06)	38 (21.22)	
5.1–10	84 (28.47)	32 (27.58)	52 (29.05)	
10.1–15	67 (22.71)	29 (25)	38 (21.22)	
15.1–20	55 (18.64)	30 (25.86)	25 (13.96)	
>20	32 (10.84)	10 (8.62)	22 (12.29)	
Mortality, *n* (%)				<0.05
Mortality	59 (15.40)	26 (22.03)	33 (12.45)	
Cardiac	22 (37.28)	5 (19.23)	17 (51.51)	
Sepsis	28 (47.45)	15 (57.69)	13 (39.39)	
Malignancy	3 (5.08)	2 (7.69)	1 (3.03)	
Cerebrovascular accident	3 (5.08)	2 (7.69)	1 (3.03)	
Pulmonary haemorrhage	1 (1.69)	0 (00)	1 (3.03)	
Hepatic failure	2 (3.38)	2 (7.69)	0 (00)	

ADPKD, autosomal dominant polycystic kidney disease; FSGS, focal segmental glomerulosclerosis; TIN, tubulointerstitial nephritis; HUS, haemolytic uraemic syndrome; IHD, ischaemic heart disease; CHF, congestive heart failure; LURD, live unrelated donor; LRD, live related donor; MMF, mycophenolate mofetil; CO, cyclosporine; PRED, prednisolone; AZA, azathioprine; SIRO, sirolimus; TAC, tacrolimus; CMV, cytomegalovirus; IQR, interquartile range.

Table 3. Factors predicting PTDM: univariate analysis

	Hazard ratio	95% CI	*p* value
Age, years	1.05	1.03–1.08	<0.05
Age at transplantation, years	1.06	1.01–2.86	<0.05
Sex (male)	1.87	1.03–3.38	<0.05
Cyclosporine	2.12	1.37–5.09	<0.05
Prednisolone	0.96	0.3–1.6	0.07
CMV seroconversion	1.39	1.14–1.49	<0.05
BK virus	0.97	0.24–1.77	0.36
HCV status	1.3	1.30–2.41	<0.05
HBV	0.94	0.35–1.88	0.86
Rejection	1.39	0.96–3.14	0.96

Table 4. Factors predicting PTDM: multivariate analysis

	Hazard ratio	95% CI	*p* value
Age, years	1.08	1.01–1.07	<0.05
Age at transplantation, years	1.08	1.03–1.09	<0.05
Sex (male)	1.7	1.15–3.92	<0.05
Cyclosporine	3.83	1.77–9.21	<0.05
CMV seroconversion	1.17	1.19–1.59	<0.05
HCV status	1.21	1.01–2.1	<0.05
Rejection	1.11	1.05–1.86	0.96

transplant recipients without affecting insulin secretion or hepatic insulin uptake [19]. HCV infection is statistically significant in our PTDM population (22.88% vs. 9.43%, p = 0.003). Allograft type is the most important allograft-associated risk factor for PTDM; Gaurishankar et al. [20] observed nearly four times higher incidence of PTDM in deceased donor allograft recipients than in live donors. In our study, 98.31% of patients had live donors, and allograft type is not associated with PTDM. Immunosuppressive regimen (induction and maintenance), cytomegalovirus infection, and number of rejection episodes are known post-transplant risk factors for PTDM. Steroids, calcineurin inhibitors (CNIs), and mammalian target of rapamycin inhibitors (mTORis) are the mainstay of immunosuppressive therapy in transplantation. Corticosteroids are used for induction (in high doses) and maintenance (lower and tapering doses) immunosuppression in renal transplantation. Hyperglycaemia and diabetes mellitus are well-known side effects of corticosteroids, and impaired insulin sensitivity, increased hepatic gluconeogenesis, and appetite stimulation leading to weight gain are the underlying mechanisms behind steroid-induced diabetes mellitus [21, 22]. The diabetic potential of the Induction protocol of corticosteroids is more than the maintenance dosage because its hyperglycaemic effect is dose-dependent [17]. Hjelmesaeth et al. [13] found a 5% increase in the risk of PTDM with a 0.01 mg/kg/day increase in the dose of prednisolone. Mathews et al. [23] also demonstrate high risk at increased dose in fix dose protocol, also there is a decrease in the incidence of PTDM with alteration of dose from high to low [24]. In our study population, Corticosteroids are the most common immunosuppressive medication used by PTDM patients as well as non-diabetic patients, and we use a fixed-dose protocol; however, its association with PTDM is statistically not significant (96.61% vs. 91.69%, p = 0.07). CNIs remain the standard of care as maintenance immunosuppression in renal transplantation for the last four decades since the discovery of cyclosporine [25]. Diabetogenic potential of CNIs is explained by impaired insulin secretion, increased islet cell apoptosis, and decreased beta cell mass [17, 26, 27]. Cyclosporine and tacrolimus are the two main CNIs used in renal transplant recipients. Webster et al. [28] illustrated in his meta-analysis of 30 randomized trials of renal transplantation that tacrolimus is more effective in preventing graft loss and acute rejection than cyclosporine; however, incidence of PTDM was greater in patients receiving tacrolimus at 1-year follow-up (RR 1.86) and increased with higher dose of tacrolimus (p = 0.003). Mathew et al. [23] observed that with every 100 ng/mL increase in trough C2 CNIs level, there is 50% increase in the risk of either post-transplant impaired glucose tolerance or PTDM. In our study population, 219 (57.18%) patients were using cyclosporine; 79 (36.07%, p = 0.009) of them developed PTDM, while 31.59% (n = 121) renal transplant recipients were

using tacrolimus, and only 33 (27%, $p = 0.308$) developed PTDM. mTORis such as sirolimus are used in combination with other immunosuppressive agents in renal transplantation and are considered an independent risk factor for PTDM development [29]. Veroux et al. [30] observed improved glycaemic control when switching cyclosporine with sirolimus in renal transplant recipients. Possible mechanisms behind mTORi-induced PTDM include impaired insulin secretion, reduced signal transduction, islet cell apoptosis (in vitro) [31]. In our study, 10.9% ($n = 42$) renal transplant recipients were using sirolimus, and 18 (42.85%, $p = 0.007$) of them developed PTDM; this association is statistically insignificant. CMV infection is common in renal transplant recipients due to its opportunistic nature and immunosuppression. Einalohi et al. [32] observed relative risk of PTDM up to 1.94 in CMV-positive renal transplant recipients than CMV-negative, hence considered independent factor for PTDM development. Definite mechanism behind CMV-induced PTDM is not clear, and it may involve islet cell destruction or pro-inflammatory cytokine production. We identified CMV infection in 23.49% ($n = 90$) of our study population, and 64.44% ($N = 58$, $p = <0.005$) developed PTDM. Renal graft rejection may predispose occurrence of PTDM. Schweer et al. [33] reported 3.98 hazard ratio for PTDM development in patients with acute cellular graft rejection; nonetheless, it is difficult to distinguish effects of rejection versus effect of anti-rejection therapy that involves high dose of steroids and CNIs. However, lesser number of patients had renal graft rejection reported in the PTDM group than non-PTDM (PTDM 26.27% vs. 28.75%, $p = 0.96$); hence, it was not risk factor in our study population. Many studies have revealed that PTDM is affiliated with increased mortality [34, 35], poor graft outcome [35, 36], and death-censored graft failure [37, 38]. Cardiovascular events, increased risk of opportunistic infection, and sepsis-related mortality are the main reasons for increased mortality in renal transplant recipients. In our renal transplant recipients, the mortality rate was 15% ($n = 59$) during the study period, and PTDM group significantly suffers higher mortality than non-PTDM renal transplant recipients (22% vs. 12.45%, $p = <0.05$). Overall, sepsis (47.45%, $n = 28$) was the most common cause of death in our transplant recipients; 15 (57.69%) of the PTDM patients and 13 (39.39%) of non-PTDM patients expired due to sepsis. Cardiac causes were the second most common reason of mortality, and non-PTDM patients have significantly more cardiac events than PTDM (51.51% vs. 19.23%).

Regarding limitations, our study is a single centre-based and pre-transplant information for some patients was not available, which precluded our analysis, for example, HBA1C data and induction therapy, as most patients had transplants outside and their data were missing. Prednisolone is a proven modifiable risk factor for PTDM; 93% of our study patients received prednisolone, and no association could be deduced between prednisolone and PTDM probably due to underpowered analysis.

Conclusion

PTDM is common among renal transplant recipients. Older age at the time of transplantation, prednisolone and cyclosporine immunosuppression, cytomegalovirus, and hepatitis C virus are risk factors. PTDM carries high mortality but is not associated with graft failure.

Statement of Ethics

This research complies with the guidelines for human studies and is conducted ethically in accordance with the Declaration of Helsinki. The study was approved by the authorized Research and Ethical Committee of Dubai. This is a retrospective observational medical study; the patient de-identified data used in this research were carried out retrospectively. Patients gave their consent to use their data for research by signing the general consent available in the medical record system.

Conflict of Interest Statement

Authors have no conflicts of interest to declare.

Funding Sources

There was no funding received by authors from any institute or commercial source.

Author Contributions

D.K. and F.J.A.: conceived the idea of research, proposal writing, and data collection; K.G.: data analysis and manuscript writing; A.A.S., H.A., M.A., S.N., and H.Y.: data collection; and M.H.R. and A.K.A.: conceived the idea of research, supervision of study, and creative input.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants, but they are available from the corresponding author (M.A.A.) upon reasonable request.

References

1 Saran R, Li Y, Robinson B, Ayanian J, Balkrishnan R, Bragg-Gresham J, et al. US Renal Data System 2014 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2015;66(1 Suppl 1): Svii, S1–305.

2 Sharif A, Hecking M, de Vries APJ, Porrini E, Hornum M, Rasoul-Rockenschaub S, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant. 2014;14(9):1992–2000.

3 American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care. 2015;38(Suppl l):S8–16.

4 World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Report of a WHO/IDF consultation. Geneva, Switzerland: World Health Organization; 2006.

5 Bashier AMK, Kumar D, Alalawi F, Al Nour H, Al Hadari AK, Bin Hussain AA, et al. Post-transplant diabetes: prevalence, risk, and management challenges. Dubai Diabetes Endocrinol J. 2022;28(3):79–92.

6 Gupta S, Pollack T, Fulkerson C, Schmidt K, Oakes DJ, Molitch ME, et al. Hyperglycemia in the posttransplant period: NODAT versus posttransplant diabetes mellitus. J Endocr Soc. 2018;2(11):1314–9.

7 Munshi VN, Saghafian S, Cook CB, Werner KT, Chakkera HA. Comparison of post-transplantation diabetes mellitus incidence and risk factors between kidney and liver transplantation patients. PLoS One. 2020; 15(1):e0226873.

8 Kuo HT, Sampaio MS, Vincenti F, Bunnapradist S. Associations of pretransplant diabetes mellitus, new-onset diabetes after transplant, and acute rejection with transplant outcomes: an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database. Am J Kidney Dis. 2010;56(6):1127–39.

9 Mannon RB. Post-Transplantation monitoring and outcomes. National kidney foundation's primer on kidney disease. 7th ed. Philadelphia (PA): Elsevier; 2018.

10 Jenssen T, Hartmann A. Emerging treatments for post-transplantation diabetes mellitus. Nat Rev Nephrol. 2015;11(8):465–77.

11 Malik RF, Jia Y, Mansour SG, Reese PP, Hall IE, Alasfar S, et al. Post-transplant diabetes mellitus in kidney transplant recipients: a multicenter study. Kidney. 2021;2(8):1296–307.

12 Ahmed SH, Biddle K, Augustine T, Azmi S. Post-transplantation diabetes mellitus. Diabetes Ther. 2020;11(4):779–801.

13 Hjelmesaeth J, Hartmann A, Kofstad J, Stenstrom J, Leivestad T, Egeland T, et al. Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. Transplantation. 1997;64(7):979–83.

14 von During ME, Jenssen T, Bollerslev J, Asberg A, Godang K, Eide IA, et al. Visceral fat is better related to impaired glucose metabolism than body mass index after kidney transplantation. Transpl Int. 2015;28(10):1162–71.

15 Walczak DA, Calvert D, Jarzembowski TM, Testa G, Sankary HN, Thielke J, et al. Increased risk of posttransplant diabetes mellitus despite early steroid discontinuation in Hispanic kidney transplant recipients. Clin Transplant. 2005;19(4):527–31.

16 Peracha J, Nath J, Ready A, Tahir S, Parekh K, Hodson J, et al. Risk of post-transplantation diabetes mellitus is greater in South Asian versus Caucasian kidney allograft recipients. Transpl Int. 2016;29(6):727–39.

17 Shivaswamy V, Boerner B, Larsen J. Post-transplant diabetes mellitus: causes, treatment, and impact on outcomes. Endocr Rev. 2016;37(1):37–61.

18 Fabrizi F, Martin P, Dixit V, Bunnapradist S, Kanwal F, Dulai G. Post-transplant diabetes mellitus and HCV seropositive status after renal transplantation: meta-analysis of clinical studies. Am J Transplant. 2005;5(10): 2433–40.

19 Baid-Agrawal S, Frei U, Reinke P, Schindler R, Kopp MA, Martus P, et al. Impaired insulin sensitivity as an underlying mechanism linking hepatitis C and posttransplant diabetes mellitus in kidney recipients. Am J Transplant. 2009;9(12):2777–84.

20 Gourishankar S, Jhangri GS, Tonelli M, Wales LH, Cockfield SM. Development of diabetes mellitus following kidney transplantation: a Canadian experience. Am J Transplant. 2004;4(11):1876–82.

21 van Raalte DH, Nofrate V, Bunck MC, van Iersel T, Elassaiss Schaap J, Nässander UK, et al. Acute and 2-week exposure to prednisolone impair different aspects of beta-cell function in healthy men. Eur J Endocrinol. 2010;162(4):729–35.

22 Yasuda K, Hines E 3rd, Kitabchi AE. Hypercortisolism and insulin resistance: comparative effects of prednisone, hydrocortisone, and dexamethasone on insulin binding of human erythrocytes. J Clin Endocrinol Metab. 1982;55(5):910–5.

23 Mathew JT, Rao M, Job V, Ratnaswamy S, Jacob CK. Post-transplant hyperglycaemia: a study of risk factors. Nephrol Dial Transplant. 2003;18(1):164–71.

24 McGeown MG, Douglas JF, Brown WA, Donaldson RA, Kennedy JA, Loughridge WG, et al. Advantages of low dose steroid from the day after renal transplantation. Transplantation. 1980;29(4):287–9.

25 Azzi JR, Sayegh MH, Mallat SG. Calcineurin inhibitors: 40 years later, can't live without. J Immunol. 2013 Dec 15;191(12):5785–91.

26 Fuji S, Kim S-W, Mori S, Furuta K, Tanosaki R, Heike Y, et al. Decreased insulin secretion in patients receiving tacrolimus as GVHD prophylaxis after allogeneic hematopoietic SCT. Bone Marrow Transplant. 2010;45:405–6.

27 Drachenberg CB, Klassen DK, Weir MR, Wiland A, Fink JC, Bartlett ST, et al. Islet cell damage associated with tacrolimus and cyclosporine: morphological features in pancreas allograft biopsies and clinical correlation. Transplantation. 1999;68(3):396–402.

28 Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. BMJ. 2005 Oct 8; 331(7520):810.

29 Gyurus E, Kaposztas Z, Kahan BD. Sirolimus therapy predisposes to new-onset diabetes mellitus after renal transplantation: a long-term analysis of various treatment regimens. Transplant Proc. 2011;43(5):1583–92.

30 Veroux M, Tallarita T, Corona D, Sinagra N, Giaquinta A, Zerbo D, et al. Conversion to sirolimus therapy in kidney transplant recipients with new onset diabetes mellitus after transplantation. Clin Dev Immunol. 2013;2013:496974.

31 Bell E, Cao X, Moibi JA, Greene SR, Young R, Trucco M, et al. Rapamycin has a deleterious effect on MIN-6 cells and rat and human islets. Diabetes. 2003;52(11):2731–9.

32 Einollahi B, Motalebi M, Salesi M, Ebrahimi M, Taghipour M. The impact of cytomegalovirus infection on new-onset diabetes mellitus after kidney transplantation: a review on current findings. J Nephropathol. 2014;3(4):139–48.

33 Schweer T, Gwinner W, Scheffner I, Schwarz A, Haller H, Blume C. High impact of rejection therapy on the incidence of post-transplant diabetes mellitus after kidney transplantation. Clin Transplant. 2014;28(4):512–9.

34 Wauters RP, Cosio FG, Suarez Fernandez ML, Kudva Y, Shah P, Torres VE. Cardiovascular consequences of new-onset hyperglycemia after kidney transplantation. Transplantation. 2012;94(4):377–82.

35 Cole EH, Johnston O, Rose CL, Gill JS. Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. Clin J Am Soc Nephrol. 2008;3(3):814–21.

36 Gaynor JJ, Ciancio G, Guerra G, Sageshima J, Hanson L, Roth D, et al. Single-centre study of 628 adult, primary kidney transplant recipients showing no unfavourable effect of new-onset diabetes after transplant. Diabetologia. 2015;58(2):334–45.

37 Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant. 2003;3(2):178–85.

38 Siraj ES, Abacan C, Chinnappa P, Wojtowicz J, Braun W. Risk factors and outcomes associated with posttransplant diabetes mellitus in kidney transplant recipients. Transplant Proc. 2010;42(5): 1685–9.