DOI: 10.5152/turkjnephrol.2026.251015

Original Article

Turkish Journal of Nephrology

Risk Factors and Clinical Implications of Post-Transplant Diabetes Mellitus: Role of Vitamin D Status

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ABSTRACT

Background: Post-transplant diabetes mellitus (PTDM) is a significant metabolic complication affecting kidney transplant recipients (KTx), contributing to increased cardiovascular morbidity, infections, graft dysfunction, and decreased survival. Understanding the risk factors associated with PTDM is essential for prevention and improved management. The aim of this study is to evaluate the association between vitamin D levels and the development of in PTDM KTx.
Methods: This retrospective cohort study included 106 KTx followed between 2005 and 2020 (median follow-up 8.1 years). Data on demographic characteristics, transplantation details, immunosuppressive regimens, dialysis history, vitamin D status, and clinical outcomes were analyzed. Logistic regression analysis identified independent predictors of PTDM.
Results: Post-transplant diabetes mellitus incidence was 25.5%. Age over 50 years (odds ratio (OR) = 1.83, 95% CI: 1.25-2.72, *P* = .036), retransplantation (OR = 2.16, 95% CI: 1.32-2.88, *P* = .009), and vitamin D deficiency (<20 ng/mL) (OR = 1.70; 95% CI: 1.25-2.72; *P* = .029) were independently associated with PTDM development. Continuous vitamin D levels, analyzed per 5 ng/mL decrease, were also significantly associated with PTDM (OR = 1.53, 95% CI: 1.09-2.25; *P* = .028). Receiver operating characteristic analysis identified serum vitamin D as the strongest predictor (AUC 0.761; sensitivity 0.72; specificity 0.68). The PTDM was associated with higher rejection episodes (37.0% vs. 15.2%, *P* = .004), increased mortality (18.5% vs. 7.5%, *P* = .012), and a trend toward higher allograft loss (25.9% vs. 12.7%, *P* = .058). Kaplan–Meier curves demonstrated consistently lower patient and graft survival in the PTDM group, although differences were not statistically significant after multivariate adjustment.
Conclusion: The PTDM occurred in one-quarter of KTx and was independently predicted by older age, retransplantation, and vitamin D deficiency.
Keywords: Kidney transplantation, PTDM, vitamin D deficiency

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Received: March 21, 2025 **Revision Requested:** May 20, 2025
Last Revision Received: September 5, 2025 **Accepted:** September 22, 2025 **Publication Date:** April 7, 2026

Cite this article as: Akgül A, Demir ME, Oguz EG, Aylı MD. Risk factors and clinical implications of post-transplant diabetes mellitus: Role of vitamin D status. *Turk J Nephrol*. 2026;35(2):118-125.

INTRODUCTION

Post-transplant diabetes mellitus (PTDM) is a significant metabolic complication that occurs in kidney transplant recipients (KTx).[1] The PTDM has been associated with increased risks of cardiovascular disease, infections, graft dysfunction, and reduced patient survival.[2,3]

Post-transplant diabetes mellitus incidence ranges from 2% to 53% in solid organ transplant recipients, depending on organ type, immunosuppressive therapy, risk factors, and follow-up duration. It is observed in 10%-20% of kidney, 20%-30% of heart, 20%-40% of lung, and 30%-40% of liver transplant recipients.[4,5]

Metabolic risk factors associated with type 2 diabetes also contribute to the PTDM development, with additional effects from immunosuppressive therapy. Risk factors for PTDM development are categorized as modifiable, including immunosuppressive drugs, viral infections, obesity, and physical inactivity, and

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non-modifiable, such as age, race, genetic predisposition, donor characteristics, family history of diabetes, prior glucose intolerance, and previous corticosteroid use.[4,6]

The pathophysiology of PTDM involves multiple mechanisms, including impaired insulin secretion, increased insulin resistance, and pancreatic beta-cell dysfunction. Immunosuppressive therapies play a central role in its development. Corticosteroids and calcineurin inhibitors (CNI) contribute to beta-cell apoptosis and impaired insulin secretion, while mTOR inhibitors exacerbate insulin resistance by increasing hepatic gluconeogenesis, reducing peripheral glucose uptake, and disrupting insulin signaling in skeletal muscle and adipose tissue. In addition to immunosuppressive agents, factors such as hypomagnesemia, hepatitis C virus infection, and cytomegalovirus (CMV) infection have also been linked to an increased risk of PTDM.[4,6]

Conflicting evidence exists regarding the role of vitamin D in diabetes mellitus development among non-transplant patients.[7,8] Kidney transplant recipients, often classified as chronic kidney disease patients, frequently exhibit low vitamin D levels. However, the impact of vitamin D on PTDM development in this population remains poorly understood.

The aim of this study is to evaluate the association between vitamin D levels and the development of in PTDM KTx, considering its potential role in glucose metabolism and insulin resistance alongside other metabolic and immunosuppressive risk factors.

MATERIAL AND METHODS

This retrospective cohort study included KTx who underwent transplantation at various hospitals in Türkiye. The diagnosis of PTDM was based on the general diabetes diagnostic criteria established by the American Diabetes Association—1) (fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) after at least 8 hours of fasting, 2) 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test, 3) hemoglobin A1c (HbA1c) ≥ 6.5%, or 4) random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) in the presence of classic symptoms of hyperglycemia (polyuria, polydipsia, weight loss) or hyperglycemic crisis.[9] However, to distinguish early post-transplant hyperglycemia from PTDM, which refers to hyperglycemia occurring within the first 45 days post-transplant, a definitive diagnosis of PTDM was made at least after 3 months transplantation.[10]

MAIN POINTS

- Post-transplant diabetes mellitus (PTDM) is a significant metabolic complication that occurs in kidney transplant recipients. Since PTDM is closely related to graft survival and mortality, it is important to identify risk factors.
- Given the potential role of vitamin D levels in glucose metabolism and insulin resistance, it plays an important role in the development of PTDM.
- Vitamin D deficiency (≤20 ng/mL) was linked to an increased risk, highlighting the potential role of vitamin D status in post-transplant glucose metabolism.
- Multicenter studies are needed to validate these results and to better understand the role of vitamin D in the prevention and management of PTDM.

The HbA1c levels were recorded, but the primary diagnostic criteria were based on persistent hyperglycemia beyond 12 weeks in previously non-diabetic individuals, along with compatible hyperglycemic symptoms. Pretransplant diabetic KTx, unknown baseline vitamin D levels within 12 weeks after transplantation, or delayed initiation of vitamin D replacement were excluded from the study. Kidney transplant recipients who survived at least 1 year were assessed.

In addition to PTDM diagnosis, participants were assessed for several demographic, clinical, and transplant-related factors.

Immunosuppressive therapy regimens were documented, including the use of CNI, with specific categorization of tacrolimus or cyclosporine use, as well as mycophenolic acid, azathioprine, and prednisolone use.

Vitamin D assessment: All KTx were routinely screened for vitamin D status every month. The average vitamin D level recorded in the 3 months following kidney transplantation was measured. Kidney transplant recipients who required vitamin D replacement followed a standard replacement protocol. A common approach for the assessment and treatment of vitamin D is as follows: Measure serum 25-hydroxyvitamin D (25(OH)D) levels to assess vitamin D status. Deficiency: <20 ng/mL (50 nmol/L), Insufficiency: 20-30 ng/mL (50-75 nmol/L), and Sufficiency: >30 ng/mL (75 nmol/L).

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical committee approval was received from the Ethics Committee of Etlik City Hospital (Approval no:AESH-BADEK-2024-1224, Date: 18.12.2024). Informed consent was waived due to the retrospective nature of the study. Patient data were anonymized and handled with strict confidentiality.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 17; IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Comparisons between the PTDM and non-PTDM groups were conducted using the independent samples *t*-test for normally distributed continuous variables and the Mann–Whitney *U*-test for non-normally distributed continuous variables. Categorical variables were compared using the chi-square (χ^2) test or Fisher's exact test, depending on expected frequencies. Univariate logistic regression analysis was performed

to identify potential risk factors for PTDM development. Variables with a *P* value <.1 in univariate analysis were included in a multivariate logistic regression model, using the stepwise regression method to determine independent predictors of PTDM, expressed as adjusted odds ratios (OR) with 95% CI. The ROC analysis, sensitivity, and specificity were calculated for different age thresholds, and the best discriminative value was identified based on Youden's Index (J = Sensitivity + Specificity − 1). A Kaplan–Meier survival analysis with the log-rank test was used to evaluate the impact of PTDM on both patient and graft survival over the follow-up period. Additionally, a Cox proportional hazards model was applied to determine independent predictors of mortality and graft loss. A *P* value <.05 was considered statistically significant in all analyses.

RESULTS

Study Cohort and Baseline Characteristics

The study dataset includes KTx who underwent transplantation between 2005 and 2020, with a mean age of 47.07 ± 10.79 years and median follow-up of 8.10 years (range 1-16 years). Overall, 73 (68.9%) were male. Post-transplant diabetes mellitus was diagnosed in 27 recipients (25.5%) a median of 6 months after transplantation (range 3-87 months) (Table 1). The most common comorbidities were hypertension (70.8%), diabetes mellitus/PTDM (35.8%), heart disease (16.0%), and cerebrovascular disease (2.4%). The primary causes of end-stage kidney disease were hypertension (31.1%), urological disorders (13.2%), diabetes mellitus (13.2%), glomerulonephritis (9.4%), and unknown causes (17.0%), with less common etiologies such as polycystic kidney disease (3.8%), urolithiasis/pyelonephritis (4.7%), familial Mediterranean fever (2.8%), and Fabry disease (0.9%). Most of the kidney transplants were from living donor kidney transplants (68.9%), while 31.1% were from deceased donor kidney transplants.

Preemptive transplantation was performed in 6.7% of patients, while 4.7% underwent retransplantation. The majority of patients (98.1%) remained on CNI-based immunosuppression; tacrolimus and mycophenolic acid were used by the majority of recipients, and all patients received prednisolone.

Comparison of Post-Transplant Diabetes Mellitus and Non-Post-Transplant Diabetes Mellitus Groups

Table 1 compares baseline characteristics between PTDM recipients (n = 27) and those without PTDM (n = 79). Age and male sex did not differ significantly. Donor type, preemptive transplantation and retransplantation rates were also comparable (*P* > .4). Rejection episodes were more frequent in PTDM recipients (37.03% vs. 15.18%; *P* = .004), and among those receiving basiliximab induction, acute rejection occurred in 5 of 6 PTDM recipients vs. 1 of 4 non-PTDM recipients (*P* = .027). Hemodialysis duration did not differ, whereas peritoneal dialysis duration was shorter in the PTDM group (32.25 ± 20.05 vs. 44.80 ± 30.54 months, *P* = .023). Prednisolone was used universally; tacrolimus and

Table 1. Comparison of Clinical and Transplant-Related Variables Between PTDM and Non-PTDM Groups

Variable	PTDM (n = 27)	Non-PTDM (n = 79)	*P*
Age (years±SD)	48.33 ± 10.00	46.76 ± 12.68	.533
Male sex, n (%)	16 (59.3)	57 (72.2)	.212
Donor type (Living), n (%)	19 (70.4)	54 (68.4)	.845
Preemptive transplantation, n (%)	1 (3.7)	6 (7.7)	.474
Retransplantation, n (%)	2 (7.4)	3 (3.8)	.445
Rejection episodes, n (%)—Total episodes	10 (37.03)	12 (15.18)	.004
Acute rejection in basiliximab users, n (%)	5/6 (83.3)	1/4 (25)	.027
Dialysis duration±SD (months)			
Hemodialysis	48.65 ± 33.60	41.08 ± 37.40	.558
Peritoneal dialysis	32.25 ± 20.05	44.80 ± 30.54	.023
Immunosuppressive regimen			
Tacrolimus use, n (%)	0 (0.0)	1 (1.3)	NA
Mycophenolic acid, n (%)	0 (0.0)	3 (3.)	.527
Prednisolone, n (%)	100	100	1.000
Basiliximab induction, n (%)	20.18 (6/27)	3.3 (2/79)	<.001
Post-transplant complications			
Delayed graft function (DGF), n (%)	6 (22.2)	13 (16.5)	.301
Biopsy-proven acute rejection, n (%)	7 (25.9)	6 (7.5)	.015
CMV positivity, n (%)	6 (22.2)	11 (13.9)	.559
BKV positivity, n (%)	5 (18.5)	20 (25.3)	.612
Malignancy, n (%)	3 (11.1)	5 (6.3)	.417
Vitamin D status			
Vitamin D level±SD (ng/mL)	15.55 ± 11.20	21.58 ± 13.47	.091
Vitamin D > 30 ng/mL (75 nmol/L), n (%)	4 (14.8)	12 (15.18)	.822
Vitamin D 20-30 ng/mL (50-75 nmol/L), n (%)	11 (40.74)	40 (51.90)	.035
Vitamin D <20 ng/mL (50 nmol/L), n (%)	12 (44.44)	27 (34.17)	.042
Last serum creatinine±SD (mg/dL)	2.21 ± 1.35	1.64 ± 0.99	.187
Mortality (exitus), n (%)	5 (18.51)	6 (7.5)	.012
Allograft loss, n (%)	7 (25.9)	10 (12.65)	.058

BKV, BK virus; CMV, cytomegalovirus; PTDM, post-transplant diabetes mellitus; SD, standart deviation

mycophenolic acid usage did not differ significantly (0 vs. 1 and 0 vs. 3, respectively; $P = .527$). Basiliximab induction was more common among PTDM recipients (20.18% vs 3.3%, $P < .001$).

Post-transplant complications were similar between groups for delayed graft function, CMV positivity, BK Virus positivity, and malignancy. Biopsy-proven acute rejection was significantly more frequent in the PTDM group (25.9% vs. 7.5%, $P = .015$). Vitamin D status differed: PTDM recipients had lower mean 25-hydroxyvitamin D concentrations (15.55 ± 11.20 vs. 21.58 ± 13.47 ng/mL, $P = .091$) and a higher prevalence of deficiency (<20 ng/mL) (44.44% vs. 34.17%, $P = .042$), whereas vitamin D insufficiency (20-30 ng/mL) was more common in non-PTDM recipients (51.90% vs. 40.74%, $P = .035$). Mortality was higher among PTDM recipients (18.51% vs. 7.5%, $P = .012$), and allograft loss tended to be more frequent (25.9% vs. 12.65%, $P = .058$), although the latter did not reach statistical significance (Table 2).

Table 2. Univariate and Multivariate Logistic Regression Analysis of Risk Factors for PTDM

	Univariate Analysis		Multivariate Analysis	
Variable	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**
Age ≥ 50 years	.018	1.59 (1.19-1.93)	.036	1.83 (1.25-2.72)
Gender, male	.072	1.48 (1.26-2.33)	.133	1.10 (1.02-1.30)
HD duration (months)	>.05	NS	.299	1.06 (0.98-1.23)
PD duration (months)	>.05	NS	>.05	NS
Deceased donor, yes	.071	1.27 (1.13-1.77)	.152	1.16 (1.03-3.08)
Vitamin D levels (per 5 ng/mL decrease)	.061	1.27 (1.02-1.82)	.028	1.53 (1.09-2.25)
Vitamin D deficiency (<20 ng/mL)	.013	1.88 (1.32-3.72)	.029	1.70 (1.17-3.42)
Retransplantation, yes	.024	1.55 (1.27-2.32)	.009	2.16 (1.32-2.88)
Preemptive transplantation, yes	>.05	NS	>.05	NS
Basiliximab induction, yes	.076	1.66 (1.09-3.12)	.119	1.06 (1.02-1.27)
CMV positivity, yes	>.05	NS	>.05	NS
Malignancy, yes	>.05	NS	>.05	NS
Exitus (mortality)	.365	NS	–	–

BKV, BK virus; CMV, cytomegalovirus; HD, hemodialysis; OR, odds ratio; PD, peritoneal dialysis.

Risk Factors for Post-Transplant Diabetes Mellitus

Univariate logistic regression identified age ≥ 50 years ($P = .018$), vitamin D deficiency (<20 ng/mL; $P = .013$) and retransplantation ($P = .024$) as significant risk factors for PTDM. These associations remained significant in multivariate analysis: age ≥ 50 years (OR = 1.83, 95% CI = 1.25-2.72; $P = .036$), vitamin D deficiency (OR = 1.70, 95% CI = 1.17-3.42; $P = .029$), and retransplantation (OR 2.16, 95% CI = 1.32-2.88; $P = .009$). Continuous vitamin D level, analyzed per 5 ng/mL decrease, also remained significant (OR = 1.53; 95% CI = 1.09-2.25; $P = .028$). Male sex, dialysis durations, deceased donor status, preemptive transplantation, basiliximab induction, CMV positivity, and malignancy were not independent predictors of PTDM in the multivariate model.

Receiver Operating Characteristic Analysis

The receiver operating characteristic (ROC) analysis (Figure 1) demonstrated that continuous serum 25-hydroxyvitamin D concentration had the strongest discriminative performance for predicting PTDM (AUC 0.761; sensitivity 0.72; specificity 0.68). Vitamin D deficiency (< 20 ng/mL) showed modest discriminative ability (AUC = 0.610; sensitivity = 0.70; specificity = 0.52), whereas age ≥ 50 years had poor discrimination (AUC = 0.571). Male sex (AUC = 0.509), retransplantation (AUC = 0.520), and basiliximab induction (AUC = 0.505) had AUC values near 0.50, indicating limited predictive utility (Table 3).

Survival Analysis

Kaplan–Meier survival analysis based on the observed event rates of allograft loss (25.9% vs. 12.7%) and mortality (18.5% vs. 7.5%) revealed a persistent survival disadvantage in the PTDM cohort. These event rates corresponded to estimated allograft survival of 75.5% and 74.1% at 5 and 10 years, respectively, for PTDM recipients, compared with 85.6% and 87.3% for non-PTDM recipients. Patient survival showed a similar divergence, with 5 and 10 year estimates of 83.2% and 81.5% in the PTDM group vs. 92.3% and 92.4% in the non-PTDM group (Table 4).

DISCUSSION

Post-transplant diabetes mellitus remains a significant metabolic complication in KTx, with multiple risk factors contributing to its development. In this study, age >50 years, retransplantation, and vitamin D deficiency were identified as independent risk factors for PTDM. These findings align with previous studies highlighting the role of age-related insulin resistance, repeated exposure to immunosuppressive agents in retransplantation, and the potential metabolic effects of vitamin D deficiency in post-transplant glucose metabolism.

Post-transplant recipient and allograft survival rates are influenced by various immunological and non-immunological factors. Among these, PTDM is a common complication.[2-5] In this study, PTDM was frequently observed, with an incidence of 25.5%, consistent with previous reports.[4,5]

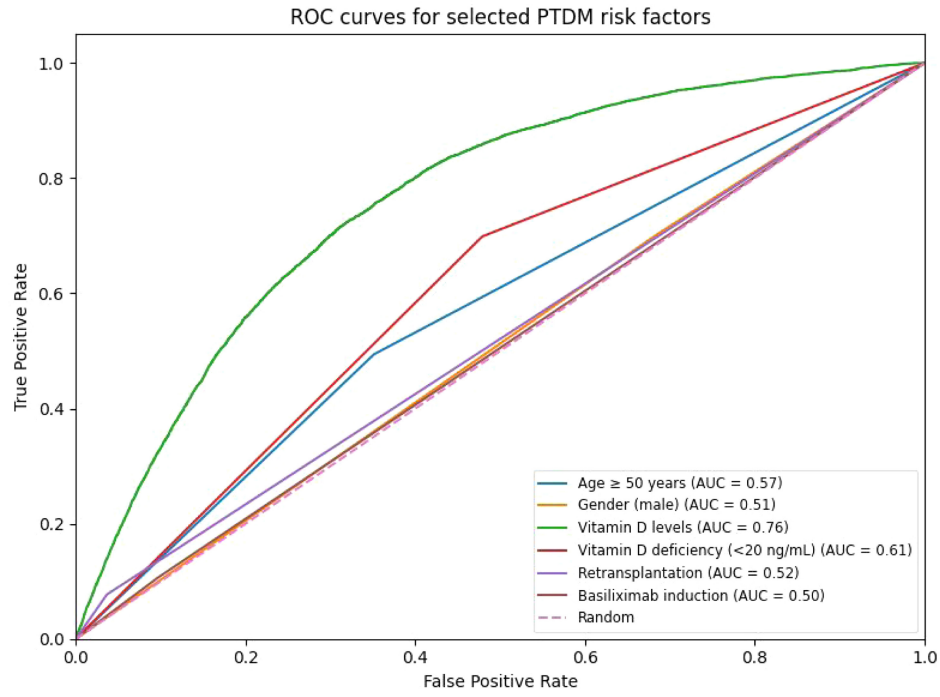

Figure 1. ROC curve for PTDM prediction.

Age is a known strong risk factor in solid organ transplantation. Post-transplant diabetes mellitus is significantly less common in children (7.1%) than adults (up to 25% by year 3), with risk increasing as transplant age rises—4.4% in children <13 years vs. 10.1% in those 13-18 years.[11] In this study, age over 50 years has increased PTDM risk 1.8 times. This effect of older age is consistent with prior studies and is likely related to age-dependent increases in insulin resistance and reduced β-cell function. These data reinforce that older transplant candidates merit careful metabolic monitoring and perhaps more aggressive management of modifiable risk factors to mitigate PTDM risk.[4-6,12]

Post-transplant diabetes mellitus occurs differently between genders, with beta-cell dysfunction being the predominant mechanism in women, likely influenced by hormonal factors, while insulin resistance and metabolic syndrome are more prominent in men.[13,4] Although PTDM appears slightly more prevalent in males, current evidence does not strongly support a significantly higher risk in men compared to women.[13] In this study, male gender showed a mild association with PTDM development in univariate analysis; however, this association was not retained in multivariate analysis, suggesting that other factors play a more significant role in PTDM risk than gender.

Patients undergoing long-term dialysis often experience chronic inflammation, oxidative stress, insulin resistance, all of which may contribute to an increased risk of PTDM. However, previous studies remain inconclusive regarding the impact of dialysis duration on PTDM development.[1,14] In this study, non-PTDM KTx had longer durations of both hemodialysis and peritoneal dialysis; however, regression analysis did not reveal a

Table 3. Receiver Operating Characteristic (ROC) Analysis of Selected Clinical Variables for Prediction of Post-Transplant Diabetes Mellitus (PTDM)

Variable	AUC	Sensitivity	Specificity
Age ≥ 50 years	0.571	0.49	0.65
Gender (male)	0.509	0.70	0.32
Vitamin D levels	0.761	0.72	0.68
Vitamin D deficiency (<20 ng/mL)	0.610	0.70	0.52
Retransplantation	0.520	0.08	0.96
Basiliximab induction	0.505	0.11	0.90

Table 4. Allograft and Patient Survival Derived from Observed Event Rates

Outcome Measure	Group	Observed Event Rate (%)	Estimated 5-Year Survival (%)	Estimated 10-Year Survival (%)
Allograft loss	PTDM	25.9	75.5	74.1
	Non-PTDM	12.7	85.6	87.3
Mortality	PTDM	18.5	83.2	81.5
	Non-PTDM	7.5	92.3	92.4

PTDM, post-transplant diabetes mellitus.

significant impact of dialysis duration on PTDM development. Interestingly, PTDM occurred more frequently in patients who had preemptive kidney transplants. It is possible that older or higher-risk patients were preferentially transplanted preemptively, confounding this association. Indeed, after adjustment for other variables, preemptive transplant was not an independent predictor of PTDM in the multivariate model. The finding may reflect selection biases or small numbers.

Patients undergoing retransplantation may be at increased risk of developing PTDM due to higher cumulative exposure to immunosuppressive therapy. Current evidence in the literature remains limited, but the data suggest a noteworthy association. In this study, PTDM was frequently observed in patients who underwent retransplantation, and regression analysis demonstrated a 2-fold increased risk of PTDM among retransplant patients. This novel finding supports the idea that the cumulative burden of immunosuppression and the complex medical history in retransplant patients can predispose them to post-transplant metabolic disturbances.

Immunosuppressive medication, specifically tacrolimus and prednisolone, has been strongly associated with PTDM development.[4,15] Tacrolimus induces β-cell toxicity by increasing oxidative stress, impairing insulin secretion, while also reducing insulin sensitivity by altering glucose metabolism in peripheral tissues.[16] Steroids, on the other hand, contribute to PTDM by inducing insulin resistance through increased hepatic gluconeogenesis, reduced glucose uptake in muscle and adipose tissue, and downregulation of insulin receptor signaling.[17] In this study, the majority of kidney transplant recipients (KTx) received tacrolimus, and no switch to cyclosporine was made in those who developed hyperglycemia. Thus, the impact of tacrolimus on PTDM development could not be checked. Similarly, although all patients were on a steroid taper to a maintenance dose, those who required high-dose corticosteroid pulses (for treatment of rejection episodes) would have had additional risk. Overall, the findings reinforce the importance of carefully balancing immunosuppressive efficacy with metabolic side effects. Where clinically feasible, using the lowest effective doses of tacrolimus and steroids, considering steroid-sparing regimens, and closely monitoring glucose can help mitigate PTDM development.

There is a bidirectional relationship between rejection and PTDM. Treatment of rejection requires more intensive immunosuppressive therapy, which ultimately increases the risk of PTDM.[4,18] Acute rejection rate was found to be 12.2% in around 9-year follow-ups in the study. Acute rejection rates were similar between PTDM and non-PTDM groups. This finding should be interpreted with caution due to the relatively limited sample size. Achieving a balance between adequate rejection control and minimization of diabetogenic therapy is a continuing challenge in post-transplant care.

An interesting observation in the study was the higher usage of basiliximab in patients who developed PTDM compared to those who did not. In a previous study, Prasad et al[19] reported that basiliximab induction may increase the risk of PTDM. However, basiliximab itself is not known to be diabetogenic, so this association likely reflects clinical decision-making and underlying risk factors. Basiliximab induction is typically reserved for patients considered at lower immunological risk, and many of these patients subsequently experienced acute rejection requiring steroid pulse therapy and intensified tacrolimus levels. The compounded immunosuppressive burden in such cases could explain the increased PTDM incidence.

Previous studies demonstrated CMV is associated with increased risk for PTDM development. It is suggested that CMV contributes to PTDM by inducing pancreatic beta-cell damage, promoting insulin resistance, and triggering immune-mediated dysfunction.[20] In this study, CMV viremia was more common among KTx with PTDM; however, in regression analysis, no impact of CMV on PTDM development was observed.

Among non-transplant patients, several studies have shown that vitamin D deficiency is associated with an increased risk of developing type 2 diabetes.[21,22] Vitamin D may enhance insulin sensitivity by regulating insulin receptor expression and contribute to glucose homeostasis by stimulating insulin secretion from pancreatic β-cells.[21-23] Previous studies demonstrated a negative effect of vitamin D deficiency on kidney transplantation by being associated with worse graft function, higher incidence of acute rejection episodes, higher incidence of proteinuria, and lower overall graft and patient survival rate.[24] However, the impact of vitamin D on PTDM development is unclear. Quach et al[25] reported that Serum 25(OH)D was an independent predictor of PTDM in KTxs. LeFur et al[26] conducted a study on 444 KTxs in a single French center, reporting a cumulative incidence of PTDM of 13.2% within the first year. Notably, patients with severe vitamin D deficiency (25[OH]D ≤ 10 ng/mL or 25 nmol/L) had a 2.41-fold higher risk of developing PTDM compared to those with sufficient vitamin D levels (≥ 30 ng/mL or 75 nmol/L). These findings suggest that profound deficiency may predispose to post-transplant dysglycemia.

In the study, the analysis of serum 25(OH)D levels as a continuous variable did not demonstrate a statistically significant association with PTDM risk; however, a trend toward lower vitamin D levels in patients who developed PTDM was observed. When considered as a continuous variable, each 5 ng/mL decrease in serum 25(OH)D level was associated with a higher risk of PTDM in multivariate analysis, though this did not reach conventional statistical significance. However, when patients were categorized by vitamin D deficiency (defined as serum 25(OH)D <20 ng/mL, a widely accepted clinical threshold), a clear pattern emerged: PTDM developed in a significantly higher proportion of vitamin D-deficient patients. Vitamin D deficiency was an independent predictor of PTDM. This finding suggests

that rather than a linear dose-response relationship across the entire range of vitamin D concentrations, it is the presence of frank deficiency that appears to confer increased susceptibility to PTDM. This distinction highlights the potential threshold effect of vitamin D, where maintaining serum levels above the deficiency cut-off may be critical in mitigating the risk. The findings align with prior studies indicating an association between vitamin D deficiency and impaired glucose metabolism in transplant recipients. However, due to the observational nature of the study, causality cannot be established, and further prospective interventional trials are warranted to clarify whether correcting vitamin D deficiency can reduce the incidence of PTDM.

Previous studies have demonstrated that PTDM is an independent and significant predictor of impaired allograft function and an increased risk of graft failure.[27,28] In the study, serum creatinine level was higher among KTx with PTDM compared to non-PTDM KTx. Despite this difference in graft function, the survival analyses did not show a statistically significant impact of PTDM on overall graft survival when adjusting for other factors. Notably, CMV infection emerged as a significant factor associated with graft loss in the cohort. This underscores the importance of infectious complications as a threat to allograft longevity.

The impact of PTDM on mortality is unclear, despite some reports suggesting PTDM-associated adverse outcomes.[29,30] In the study, the exitus rate was higher in the PTDM group; however, there was no impact of PTDM on mortality in regression analysis. These results imply that, within the cohort, PTDM by itself did not definitively shorten patient lifespan post-transplant once other factors were accounted for. It is possible that the increased mortality observed in univariate analysis was due to PTDM patients being older or having more comorbid conditions (factors that were adjusted for in multivariate analysis). The findings are in line with some reports that failed to show PTDM as an independent mortality risk, especially in studies with relatively small sample sizes or shorter follow-up.

The study has several limitations. First, its retrospective and single-center design inherently limits generalizability and introduces the possibility of selection bias. The relatively small sample size reduces statistical power and may have contributed to some associations not reaching significance, such as the trends observed for vitamin D levels, graft loss, and survival outcomes. In addition, the follow-up period, although reasonably long (median 8.1 years), may still be insufficient to fully capture the long-term impact of PTDM on graft and patient survival.

Second, certain clinical and metabolic risk factors were not available, including body mass index, family history of diabetes, and hepatitis C virus infection, all of which are known to influence PTDM risk. These limitations emphasize the need for larger, multicenter, prospective studies with comprehensive data collection to validate the findings and clarify the role of modifiable factors such as vitamin D deficiency in PTDM development.

In conclusion, this study identified age over 50 years, retransplantation, and vitamin D deficiency as independent risk factors for the development of PTDM in KTx. Although lower vitamin D levels alone were not significantly associated with PTDM, vitamin D deficiency (≤20 ng/mL) was linked to an increased risk, highlighting the potential role of vitamin D status in post-transplant glucose metabolism. Additionally, PTDM was associated with poorer graft function, higher rates of CMV infection, malignancy, and mortality. These findings emphasize the importance of early identification and monitoring of high-risk patients, optimizing immunosuppressive strategies, and addressing modifiable risk factors, including vitamin D deficiency, to reduce the burden of PTDM and improve long-term outcomes in KTx. Further prospective, multicenter studies are needed to validate these results and to better understand the role of vitamin D in the prevention and management of PTDM.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no Artificial Intelligence tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Etlik City Hospital (Approval no:AESH-BADEK-2024-1224, Date: 18.12.2024).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.A.; Design – A.A.; Supervision – M.E.D., M.D.A.; Resources – E.G.O.; Data Collection and/or Processing – E.G.O.; Analysis and/or Interpretation – A.A., M.E.D.; Literature Search – M.E.D., A.A.; Writing Manuscript – M.E.D., A.A.; Critical Review – M.D.A., M.E.D., E.G.O.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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