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Short-Term Efficacy and Safety of Basal-Bolus Insulin Regimens in Renal Transplant Recipients With Pre-existing Type 2 Diabetes Mellitus in Early Post-transplant Outpatient Settings

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Abstract

Introduction

Glycemic control is important for allograft and patient survival in renal transplant recipients. We evaluated short-term treatment outcomes of basal-bolus insulin regimens during outpatient diabetes management in renal transplant recipients with pre-existing diabetes.

Materials and methods

In this 24-week retrospective observational study, 112 adults with pre-existing type 2 diabetes mellitus (T2DM) who underwent renal transplantation were evaluated for changes in HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), serum creatinine, estimated glomerular filtration rate (eGFR), body weight, and hypoglycemic episodes during 24 weeks of outpatient management with basal-bolus insulin regimens.

Results

Basal-bolus insulin therapy was associated with significant reductions in mean HbA1c (8.9% to 7.2%; $p < 0.001$), FPG (237.9 to 122.3 mg/dL; $p < 0.001$), and PPG (342.2 to 173.0 mg/dL; $p < 0.001$). Overall, 45.5% of patients achieved HbA1c ⩽7%, while 46.4% achieved HbA1c >7% and <8%. Body weight increased modestly (mean weight gain of 1.24 kg), with numerically greater weight gain in the glargine group, although the difference was not statistically significant in the primary analysis ($p = 0.061$). No statistically significant differences in glycemic or renal outcomes were observed between the degludec and glargine groups or between the regular human insulin and insulin aspart groups. Nocturnal hypoglycemia occurred in four of 60 (6.7%) patients receiving degludec and seven of 52 (13.5%) patients receiving glargine; however, the difference was not statistically significant ($p = 0.341$).

Conclusions

Glycemic control improved over 24 weeks among renal transplant recipients with pre-existing T2DM receiving basal-bolus insulin therapy, without deterioration in measured renal function parameters. No statistically significant differences in glycemic outcomes or the proportions of patients experiencing nocturnal hypoglycemia were observed between the degludec and glargine groups.

Categories: Transplantation, Internal Medicine, Endocrinology/Diabetes/Metabolism
Keywords: basal-bolus insulin regimen, insulin degludec, insulin glargine, post-transplant diabetes management, type 2 diabetes mellitus

Introduction

Diabetes is the leading cause of chronic kidney disease (CKD), accounting for approximately 25-30% of cases of end-stage renal disease (ESRD) [1-4]. Renal transplantation is the definitive treatment for ESRD and is the most commonly performed solid organ transplantation [5]. Regardless of previous glycemic status, transplant recipients are at risk of postoperative hyperglycemia due to surgical stress, recovering renal function, and the use of immunosuppressants and corticosteroids [6,7]. Immunosuppressive agents such as tacrolimus can adversely affect pancreatic insulin synthesis and secretion and interfere with the peripheral action of insulin [8-10]. Glucocorticoids adversely affect glucose metabolism by increasing hepatic gluconeogenesis and reducing peripheral tissue sensitivity to insulin [11].

Good glycemic control is essential for renal allograft and patient survival in renal transplant recipients with type 2 diabetes mellitus (T2DM) [12]. Glycemic control can be highly variable during the early post-

transplant period because of surgical stress, rapid fluctuations in renal function, and frequent alterations in immunosuppressant and corticosteroid doses, leading to changes in insulin secretion and insulin resistance [13]. Both pre-transplant and post-transplant diabetes are risk factors for myocardial infarction after renal transplantation [14]. Achieving good glycemic control is also important for reducing the risk of microvascular complications, particularly adverse renal outcomes, in renal transplant recipients with diabetes [10,15].

The UK Prospective Diabetes Study found that most patients with T2DM required insulin within nine years of diabetes diagnosis because of progressive loss of β-cell function [16]. Consequently, many patients with long-standing diabetes and ESRD undergoing renal transplantation may require intensification to a basal-bolus insulin regimen. However, evidence regarding glycemic management during the early post-transplant period in recipients with pre-existing diabetes remains limited. Therefore, this retrospective observational study evaluated changes in glycemic control, with the change in HbA1c from baseline to week 24 as the primary outcome, among renal transplant recipients with pre-existing T2DM receiving degludec- or glargine-based basal-bolus insulin regimens in an outpatient endocrinology setting. Additional outcomes included fasting and postprandial plasma glucose (PPG), renal function, body weight, and hypoglycemia, with exploratory comparisons between insulin regimens.

A preliminary analysis of a subset of the study population was previously presented as an abstract at the 59th Annual Meeting of the European Association for the Study of Diabetes, held in Hamburg, Germany, from October 2 to 6, 2023.

Materials And Methods

Study population

This single-center retrospective observational study reviewed the clinical records of adults (>18 years) with pre-existing T2DM who underwent renal transplantation and were referred by the renal transplant team to the endocrinology outpatient department (OPD) between January 1, 2018, and November 30, 2019. Records of consecutive eligible patients with at least 24 weeks of available follow-up were retrospectively evaluated. Eligibility was not restricted by the underlying cause of ESRD; patients with diabetic nephropathy and other causes of ESRD were eligible, provided they had pre-existing T2DM. Only patients with no history of graft rejection who were receiving corticosteroid therapy were included. The retrospective analysis was based on clinical records available from the endocrinology OPD following referral; comprehensive pre-transplant clinical records were not available to the study team.

No formal a priori sample size calculation was performed, as the study population was determined by the availability of eligible clinical records during the defined study period. The endocrinology OPD operated six days per week, excluding Sundays. Consecutive eligible patients referred by the renal transplant team during the study period were included.

The study protocol was reviewed by the Narayana Health Rabindranath Tagore International Institute of Cardiac Sciences Ethics Committee, Kolkata, which granted an exemption from ethics review (approval number: NHRTIICSEC/INV/Non-Reg/2025/005; approval date: April 1, 2025) for the retrospective data acquisition and analysis undertaken for the present study.

Immunosuppressive therapy

All patients received renal allografts from living donors, either related or unrelated. Immunosuppressive therapy comprised tacrolimus (initial dose, 0.15 mg/kg), with target trough blood levels of 10-15 ng/mL during months 1-3 and 5-10 ng/mL during months 3-6, and prednisolone (20 mg/day), gradually tapered by 2.5 mg/month to a target dose of 5 mg/day by the end of six months. All patients also received mycophenolate mofetil (1.5 g/day). Episodes of acute allograft rejection were treated with intravenous methylprednisolone 1 g/day for three consecutive days.

Initiation and maintenance of immunosuppressive therapy were managed by the renal transplant team during the perioperative period and by the nephrology OPD following discharge. Neither the renal transplant team nor the nephrology OPD consultants were part of the study group.

Study outcome measures

Baseline was defined as the first recorded assessment at the endocrinology OPD following referral after renal transplantation. The available clinical records were evaluated for fasting plasma glucose (FPG), PPG, HbA1c, body weight, serum creatinine, estimated glomerular filtration rate (eGFR), and hypoglycemic episodes over the 24-week follow-up period. The principal outcome evaluated was the change in HbA1c from baseline to week 24. Additional glycemic outcomes included changes in FPG and PPG and the proportions of patients achieving HbA1c ⩽7.0% (⩽53 mmol/mol), >7.0% to <8.0% (>53 to <64 mmol/mol), and ⩾8.0% (⩾64 mmol/mol). Safety assessments included changes in body weight, serum creatinine, eGFR, and the occurrence of hypoglycemia.

Documented symptomatic hypoglycemia was defined as an event accompanied by symptoms of hypoglycemia and a confirmatory blood glucose value ≤70 mg/dL. As hypoglycemia was assessed retrospectively, ascertainment was limited to events documented in the clinical records, and nocturnal or asymptomatic episodes without recorded glucose measurements may have been missed. Clinically significant hypoglycemia was defined as a blood glucose value <54 mg/dL. Severe hypoglycemia was defined as an event requiring assistance from another person to administer carbohydrate, glucagon, or other resuscitative measures. Confirmed hypoglycemia included documented symptomatic or asymptomatic episodes with a blood glucose value ≤70 mg/dL and severe events, if any. Hypoglycemia occurring between 00:00 and 05:59 hours was classified as nocturnal.

Diabetes management and insulin titration

As part of routine institutional practice, patients were referred by the renal transplant team for follow-up at the endocrinology OPD within two weeks of hospital discharge following renal transplantation. At the endocrinology OPD, all patients were managed with basal-bolus insulin therapy comprising either insulin degludec or insulin glargine as basal insulin and either regular human insulin or insulin aspart as prandial insulin. Degludec was preferred owing to its lower risk of hypoglycemia, although patient affordability also influenced basal insulin selection. Treatment decisions were made as part of routine clinical care rather than through random allocation. As part of routine clinical management, insulin degludec and glargine were administered at the same time each day. Standard recommended dosing and titration schedules were used as part of routine clinical care to individualize the insulin dose for each patient. In basal-insulin-naïve patients, basal insulin was initiated at 10 units once daily. Dose titration was performed according to the standard titration algorithm for ambulatory management of T2DM (Table *1*).

Pre-breakfast plasma glucose, mg/dL*	Basal insulin dose adjustment, units
<80†	−2
80-130	0
131-160	+2
161-180	+4
>180	+6

TABLE 1: Pre-defined titration algorithm for insulin dose

*Mean of three consecutive days' measurements. †Unless there is an obvious explanation for the low value, such as a missed meal.

The basal insulins prescribed were insulin degludec 100 U/mL and insulin glargine 100 U/mL, both administered using 3-mL prefilled insulin pens. Degludec and glargine were injected subcutaneously in the abdomen, upper arm (deltoid area), or thigh; injection sites were rotated within the injection areas as part of routine clinical care.

As part of routine clinical care, basal insulin was titrated to achieve a pre-breakfast self-measured plasma glucose (SMPG) concentration of 80-130 mg/dL, based on the average of three consecutive pre-breakfast SMPG values and the most recent basal insulin dose. Prandial insulin was titrated after adjustment of the basal insulin dose. Routine post-transplant follow-up was scheduled weekly during the first month, every two weeks from weeks 4 to 12, and every four weeks from weeks 12 to 24. Prandial insulin titration followed a standard glucose-guided insulin adjustment approach. Patients were advised to obtain at least two seven-point blood glucose profiles per week through self-monitoring to guide insulin dose adjustments.

Statistical analysis

Data were summarized using appropriate descriptive statistics. Continuous variables were expressed as mean ± standard deviation (SD) and median with the interquartile range (IQR), as appropriate. Categorical variables were summarized as frequencies and percentages. Within-group changes from baseline to week 24 were evaluated using the paired-samples Student's t-test (primary analysis) and the Wilcoxon signed-rank test (supplementary analysis). Between-group comparisons of continuous variables were performed using Welch's independent-samples t-test (primary analysis) and the Mann-Whitney U test (supplementary analysis). Changes for between-group comparisons were calculated by subtracting baseline values from week 24 values. Comparisons of continuous variables across more than two independent groups were performed using the Kruskal-Wallis test, as appropriate. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Fisher's exact test was used for hypoglycemia comparisons because of small event counts, and unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. The chi-square test for trend was used where applicable. eGFR was calculated using the 2021 Chronic Kidney

Disease Epidemiology Collaboration (CKD-EPI) creatinine equation; eGFR analyses included 111 patients because age data were unavailable for one patient. Associations between tacrolimus concentrations and clinical outcomes were evaluated using Spearman's rank correlation coefficient. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed using GraphPad Prism version 8 (GraphPad Software, LLC, Boston, MA, USA) and SPSS Statistics version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY).

Results

Baseline characteristics

Data from all 112 patients were included in the analysis. The mean age was 53.41 ± 8.68 years (n = 111), and the mean duration of diabetes was 14.41 ± 5.71 years. The majority of patients (83.93%; n = 94) were male. Baseline glycemic control was poor, with a mean HbA1c approaching 9% and markedly elevated fasting and postprandial glucose levels, indicating the need for intensive insulin therapy.

Overall outcomes of basal-bolus insulin therapy

Glycemic control improved significantly over the 24-week follow-up, with reductions in HbA1c, FPG, and PPG (Table 2). Serum creatinine decreased, while eGFR increased during follow-up. Improvements in glycemic control were also observed across clinically relevant subgroups, including sex, basal insulin type (degludec or glargine), and prandial insulin type (regular human insulin or insulin aspart). Tacrolimus concentration measurements were available for 96 patients at baseline and 92 patients at week 24. The mean concentrations were 14.99 ± 7.45 ng/mL and 9.25 ± 5.60 ng/mL, respectively.

Parameter	Baseline (mean ± SD)	Week 24 (mean ± SD)	Paired t	p-value	Baseline (median (Q1-Q3))	Week 24 (median (Q1-Q3))	Wilcoxon W	p-value
FPG, mg/dL	237.9 ± 75.7	122.3 ± 22.3	16.9	<0.001	212.0 (179.8-287.3)	119.0 (108.8-135.0)	1.0	<0.001
PPG, mg/dL	342.2 ± 103.6	172.9 ± 40.9	16.9	<0.001	332.5 (261.0-402.3)	167.5 (145.0-192.0)	36.0	<0.001
HbA1c, %	8.9 ± 1.2	7.2 ± 0.7	21.1	<0.001	8.6 (8.1-9.3)	7.1 (6.8-7.5)	0.0	<0.001
Weight, kg	65.4 ± 7.6	66.6 ± 7.1	−12.4	<0.001	66.0 (60.0-70.0)	67.0 (62.0-70.3)	32.0	<0.001
Creatinine, mg/dL	1.61 ± 0.72	1.37 ± 0.71	3.1	0.002	1.45 (1.09-1.9)	1.2 (0.97-1.6)	1423.5	<0.001
eGFR, mL/min/1.73 m²	59.1 ± 24.7	68.8 ± 23.8	−4.4	<0.001	56.8 (39.3-77.8)	68.6 (49.8-87.3)	1441.0	<0.001

TABLE 2: Baseline vs. week 24 comparison of FPG, PPG, HbA1c, weight, creatinine, and eGFR

Data are presented as mean ± SD and median (Q1-Q3). Changes from baseline to week 24 were assessed using the paired-samples t-test and Wilcoxon signed-rank test. Paired t-statistics were calculated using baseline minus week 24 values. eGFR was calculated using the 2021 CKD-EPI creatinine equation and was available for 111 patients; all other analyses included 112 patients. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

FPG: fasting plasma glucose, PPG: postprandial plasma glucose, HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, SD: standard deviation, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

Significant improvements in glycemic parameters were observed in both the degludec and glargine groups. However, in the primary analysis, the reduction in serum creatinine reached statistical significance only in the degludec group (Tables 3-4).

Parameter	Baseline (mean ± SD)	Week 24 (mean ± SD)	Paired t	p-value	Baseline (median (Q1-Q3))	Week 24 (median (Q1-Q3))	Wilcoxon W	p-value
FPG, mg/dL	231.7 ± 76.3	123.3 ± 23.6	11.4	<0.001	207.5 (164.5-284.0)	120.5 (110.5-135.0)	1.0	<0.001
PPG, mg/dL	330.2 ± 106.3	178.3 ± 43.2	11.1	<0.001	312.0 (255.5-369.5)	170.0 (149.3-196.0)	10.0	<0.001
HbA1c, %	8.9 ± 1.2	7.2 ± 0.7	16.1	<0.001	8.6 (8.1-9.4)	7.2 (6.7-7.5)	0.0	<0.001
Weight, kg	65.9 ± 7.3	66.9 ± 7.1	−8.3	<0.001	66.0 (61.8-70.0)	67.0 (62.0-71.0)	12.0	<0.001
Creatinine, mg/dL	1.5 ± 0.6	1.29 ± 0.52	2.61	0.011	1.4 (1.09-1.84)	1.20 (0.96-1.52)	412.5	<0.001
eGFR, mL/min/1.73 m²	61.2 ± 24.3	71.8 ± 24.1	−3.4	0.001	57.9 (41.9-81.4)	68.3 (53.2-96.5)	413.0	<0.001

TABLE 3: Baseline vs. week 24 comparison of FPG, PPG, HbA1c, weight, creatinine, and eGFR for patients on Degludec (N = 60)

Data are presented as mean ± SD and median (Q1-Q3). Changes from baseline to week 24 were assessed using the paired-samples t-test and Wilcoxon signed-rank test. Paired t-statistics were calculated as baseline minus week 24 values. eGFR was calculated using the 2021 CKD-EPI creatinine equation. All analyses included 60 patients. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

FPG: fasting plasma glucose, PPG: postprandial plasma glucose, HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, SD: standard deviation, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

Parameter	Baseline (mean ± SD)	Week 24 (mean ± SD)	Paired t	p-value	Baseline median (Q1-Q3)	Week 24 median (Q1-Q3)	Wilcoxon W	p-value
FPG, mg/dL	245.1 ± 75.1	121.1 ± 20.8	12.5	<0.001	214.5 (189.0-299.3)	118.5 (108.0-131.5)	0.0	<0.001
PPG, mg/dL	356.1 ± 99.6	166.8 ± 37.4	13.4	<0.001	351.0 (288.5-412.8)	166.5 (137.5-190.3)	5.0	<0.001
HbA1c, %	8.8 ± 1.2	7.2 ± 0.6	13.6	<0.001	8.6 (8.1-9.2)	7.100 (6.8-7.6)	0.0	<0.001
Weight, kg	64.7 ± 7.9	66.1 ± 7.2	−9.4	<0.001	64.5 (60.0-70.0)	66.000 (61.8-70.0)	4.5	<0.001
Creatinine, mg/dL	1.71 ± 0.85	1.45 ± 0.88	1.94	0.057	1.53 (1.13-2.19)	1.200 (0.99-1.66)	308.5	<0.001
eGFR, mL/min/1.73 m²	56.6 ± 25.1	65.2 ± 23.2	−2.87	0.006	56.1 (34.8-76.5)	68.6 (46.6-80.8)	325.0	0.003

TABLE 4: Baseline vs. week 24 comparison of FPG, PPG, HbA1c, weight, creatinine, and eGFR for patients on Glargine (N = 52)

Data are presented as mean ± SD and median (Q1-Q3). Changes from baseline to week 24 were assessed using the paired-samples t-test and Wilcoxon signed-rank test. Paired t-statistics were calculated as baseline minus week 24 values. eGFR was calculated using the 2021 CKD-EPI creatinine equation. Analyses included 52 patients, except for eGFR (n = 51), because age data were unavailable for one patient. Wilcoxon W represents the smaller signed-rank sum as reported by the two-sided test. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

FPG: fasting plasma glucose, PPG: postprandial plasma glucose, HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, SD: standard deviation, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

Fifty-one (45.54%) patients achieved HbA1c ⩽7%, while 52 (46.43%) had HbA1c >7% to <8%, and the remaining nine (8.04%) had HbA1c ⩾8%. Across week 24 HbA1c categories (⩾8%, >7% and <8%, and ⩽7%), there was no significant difference in the distribution of diabetes duration ($p = 0.773$; Kruskal-Wallis test).

Basal-bolus insulin therapy was associated with substantial improvements in glycemic control over the 24-week follow-up. Serum creatinine decreased, and eGFR increased over the 24-week follow-up period, with no evidence of deterioration in renal function based on these parameters.

Comparison of basal insulin: degludec and glargine groups

There were no significant differences in baseline or week 24 HbA1c, FPG, PPG, serum creatinine, or eGFR between the degludec (n = 60) and glargine (n = 52) groups (Table 5).

Parameter	Degludec mean ± SD	Glargine mean ± SD	Welch t(df)	p-value	Degludec median (Q1-Q3)	Glargine median (Q1-Q3)	Mann-Whitney U	p-value
Age, years	52.7 ± 8.4	54.2 ± 8.9	−0.9 (103.7)	0.375	53.0 (48.0-57.3)	56.00 (47.50-62.00)	1342.0	0.267
Weight, baseline, kg	65.9 ± 7.3	64.7 ± 7.9	0.9 (104.7)	0.397	66.0 (61.8-70.0)	64.50 (60.00-70.00)	1716.5	0.362
Weight, week 24, kg	66.9 ± 7.1	66.1 ± 7.2	0.6 (107.1)	0.533	67.0 (62.0-71.0)	66.00 (61.75-70.00)	1669.0	0.526
Weight change, kg	1.07 ± 1.00	1.45 ± 1.11	−1.9 (103.6)	0.061	1.0 (0.0-2.0)	2.0 (0.0-2.0)	1228.0	0.045
Total daily insulin dose, U/day	62.8 ± 25.6	65.3 ± 22.2	−0.6 (108.0)	0.577	57.0 (45.5-78.0)	62.0 (46.0-79.5)	1387.5	0.485
FPG, baseline, mg/dL	231.7 ± 76.3	245.1 ± 75.1	−0.9 (108.2)	0.350	207.5 (164.5-284.0)	214.50 (189.0-299.3)	1370.0	0.269
FPG, week 24, mg/dL	123.3 ± 23.6	121.1 ± 20.8	0.5 (110.0)	0.601	120.5 (110.5-135.0)	118.5 (108.0-131.5)	1647.0	0.614
PPG, baseline, mg/dL	330.2 ± 106.3	356.1 ± 99.6	−1.3 (109.3)	0.187	312.0 (255.5-369.5)	351.0 (288.5-412.8)	1252.0	0.073
PPG, week 24, mg/dL	178.3 ± 43.2	166.9 ± 37.4	1.5 (110.0)	0.136	170.0 (149.3-196.0)	166.5 (137.5-190.3)	1706.0	0.396
HbA1c, baseline, %	8.9 ± 1.2	8.84 ± 1.17	0.4 (107.5)	0.720	8.55 (8.10-9.40)	8.60 (8.10-9.20)	1637.0	0.655
HbA1c, week 24, %	7.2 ± 0.7	7.22 ± 0.63	−0.3 (109.4)	0.775	7.20 (6.70-7.50)	7.10 (6.80-7.60)	1501.5	0.735
HbA1c change, %	−1.74 ± 0.84	−1.62 ± 0.86	−0.7 (106.7)	0.478	−1.70 (−2.10--1.10)	−1.40 (−2.00--1.10)	1387.5	0.315
Creatinine, baseline, mg/dL	1.53 ± 0.59	1.71 ± 0.85	−1.3 (89.8)	0.192	1.43 (1.09-1.84)	1.53 (1.13-2.19)	1420.5	0.417
Creatinine, week 24, mg/dL	1.30 ± 0.52	1.45 ± 0.88	−1.1 (80.2)	0.261	1.20 (0.95-1.52)	1.20 (0.99-1.65)	1446.0	0.508
Creatinine change, mg/dL	−0.23 ± 0.68	−0.26 ± 0.95	0.17 (91.0)	0.868	−0.14 (−0.40-0.00)	−0.22 (−0.49-0.00)	1691.5	0.445
eGFR, baseline, mL/min/1.73 m²	61.2 ± 24.3	56.6 ± 25.1	0.9 (104.9)	0.332	57.9 (41.9-81.4)	56.1 (34.8-76.5)	1678.0	0.383
eGFR, week 24, mL/min/1.73 m²	71.8 ± 24.1	65.2 ± 23.2	1.4 (107.3)	0.149	68.3 (53.2-96.5)	68.6 (46.6-80.8)	1725.0	0.250
eGFR change, mL/min/1.73 m²	10.6 ± 24.4	8.7 ± 21.6	0.45 (108.8)	0.656	6.77 (−0.44-21.31)	12.23 (−0.32-21.29)	1476.5	0.754

TABLE 5: Baseline and week 24 comparison of FPG, PPG, HbA1c, weight, creatinine, eGFR, and TDI between degludec (N = 60) and glargine (N = 52) groups

Data are presented as mean ± SD and median (Q1–Q3). Between-group comparisons were performed using Welch's independent-samples t-test (primary analysis) and the Mann-Whitney U test (supplementary analysis). Change was calculated as week 24 minus baseline. All statistical tests were two-sided, with $p < 0.05$ considered statistically significant.

The overall cohort comprised 112 patients (insulin degludec, n = 60; insulin glargine, n = 52). Age and eGFR were available for 111 patients (60 and 51, respectively). Total daily insulin dose was evaluable for 110 patients (59 and 51, respectively). eGFR was calculated using the 2021 CKD-EPI creatinine

equation.

FPG: fasting plasma glucose, PPG: postprandial plasma glucose, HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, SD: standard deviation, Q1: first quartile, Q3: third quartile, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

There was no significant difference in the proportion of patients reaching target HbA1c, with a similar distribution across the week 24 HbA1c categories (⩽7%, >7% to <8%, and ⩾8%) between the degludec and glargine groups. Weight gain was numerically greater in the glargine group; Welch's independent-samples t-test did not show a statistically significant difference (p = 0.061), whereas the Mann-Whitney U test showed a significant difference (p = 0.045). Total daily insulin dose did not differ significantly between the groups (Table 5).

Comparison of prandial insulin: regular human insulin and insulin aspart groups

There were no significant differences between patients receiving regular human insulin and those receiving insulin aspart in glycemic parameters, renal parameters, body weight, or achievement of HbA1c targets (all p > 0.05). No statistically significant differences in these measured outcomes were observed according to the type of prandial insulin used.

Incidence of hypoglycemia

Hypoglycemia was recorded in 20 of 112 patients (17.9%), including nine of 60 patients (15.0%) receiving insulin degludec and 11 of 52 patients (21.2%) receiving insulin glargine (OR 0.66, 95% CI 0.22-1.94; Fisher's exact p = 0.463). Nocturnal hypoglycemia was numerically less frequent with insulin degludec than with insulin glargine (6.7% vs. 13.5%; OR 0.46, 95% CI 0.09-1.95; p = 0.341). Daytime hypoglycemia occurred in five (8.3%) and four (7.7%) patients, respectively (OR 1.09, 95% CI 0.22-5.82; p = 1.000). None of the between-group comparisons reached statistical significance. One severe hypoglycemic episode was documented in a patient receiving insulin glargine (Table 6).

Hypoglycemia outcome	Degludec (N = 60), n (%)	Glargine (N = 52), n (%)	Unadjusted OR (95% CI)	Fisher's exact p-value
Any hypoglycemia	9 (15.0)	11 (21.2)	0.66 (0.22-1.94)	0.463
Daytime hypoglycemia	5 (8.3)	4 (7.7)	1.09 (0.22-5.82)	1
Nocturnal hypoglycemia	4 (6.7)	7 (13.5)	0.46 (0.09-1.95)	0.341
Severe hypoglycemia	0 (0.0)	1 (1.9)	-	-

TABLE 6: Comparison of hypoglycemia outcomes between insulin degludec and insulin glargine groups

Values are presented as the number and percentage of patients experiencing hypoglycemia. ORs compare insulin degludec with insulin glargine (reference group) and are presented with exact conditional 95% CIs. Between-group comparisons were performed using two-sided Fisher's exact tests. Daytime hypoglycemia includes recorded pre-lunch and pre-dinner hypoglycemia. Counts represent patients with documented hypoglycemia rather than the total number of episodes. The single severe hypoglycemic event occurred in the glargine group and is included within the overall hypoglycemia count. A p-value <0.05 was considered statistically significant.

OR: odd ratios, CI: confidence interval

Across the four recorded hypoglycemia categories (no hypoglycemia, pre-lunch, pre-dinner, and nocturnal hypoglycemia; n = 92, 6, 3, and 11, respectively), Kruskal-Wallis testing showed no significant differences in age (H(3) = 3.248, p = 0.355), total daily insulin dose (H(3) = 1.296, p = 0.730), baseline weight (H(3) = 1.420, p = 0.701), FPG (H(3) = 0.796, p = 0.850), PPG (H(3) = 5.305, p = 0.151), HbA1c (H(3) = 1.059, p = 0.787), or serum creatinine (H(3) = 7.323, p = 0.062). Baseline eGFR differed across categories (H(3) = 9.720, p = 0.021).

At week 24, there were no significant differences in weight (H(3) = 1.730, p = 0.630), FPG (H(3) = 5.835, p = 0.120), PPG (H(3) = 1.733, p = 0.630), or HbA1c (H(3) = 1.823, p = 0.610). However, serum creatinine (H(3) = 27.126, p < 0.001) and eGFR (H(3) = 28.794, p < 0.001) differed significantly across categories. Changes in HbA1c (H(3) = 1.518, p = 0.678) and creatinine (H(3) = 6.988, p = 0.072) were not significantly different, whereas the change in eGFR showed a nominally significant difference (H(3) = 8.001, p = 0.046).

These exploratory findings should be interpreted cautiously because of the small hypoglycemia subgroups,

particularly the pre-dinner category (n = 3), and the multiple comparisons performed. No adjustment for multiple testing was applied.

Associations between tacrolimus concentrations and clinical outcomes

Exploratory Spearman correlation analysis showed no significant association between the baseline tacrolimus concentration and the change in HbA1c (ρ = 0.068, p = 0.508; n = 96) or the change in eGFR (ρ = 0.078, p = 0.450; n = 96). The week 24 tacrolimus concentration showed a significant inverse correlation with the change in HbA1c (ρ = −0.257, p = 0.013; n = 92), but not with the change in eGFR (ρ = 0.059, p = 0.576; n = 92). Neither the baseline nor the week 24 tacrolimus concentration was significantly associated with total daily insulin dose. These exploratory associations do not establish a causal relationship between tacrolimus exposure and glycemic or renal outcomes.

Discussion

Diabetes continues to be a major contributor to the global burden of ESRD [1-4]. Renal transplantation is the definitive treatment for ESRD and is the most commonly performed solid organ transplantation [5]. Because of the high prevalence of diabetes among the general population in India, there is a growing population of patients with CKD. Diabetes is a risk factor for poor outcomes among renal transplant recipients [10,15]. Transplant recipients are predisposed to insulin resistance, hypertension, and hyperlipidemia, which, together with hyperglycemia, promote atherosclerosis and increase cardiovascular morbidity and mortality, as well as the risk of infections [15,17,18]. Patients with diabetes undergoing renal transplantation, irrespective of their preoperative glycemic status, are susceptible to significant but variable postoperative hyperglycemia due to surgical stress, recovery of renal function, and rapidly changing doses of corticosteroids and immunosuppressants, making it challenging to achieve glycemic targets after transplantation. Poor glycemic control is associated with poor graft and patient survival in patients with T2DM [18,19]. Current Kidney Disease: Improving Global Outcomes (KDIGO) guidance recommends individualized HbA1c targets in patients with diabetes and CKD not treated with dialysis, generally ranging from <6.5% to <8.0%, with the target selected according to patient-specific factors and the risk of hypoglycemia [20].

In our study, patients with diabetes and ESRD who underwent renal transplantation had a mean diabetes duration of 14.41 ± 5.71 years and received basal-bolus insulin therapy. There are limited data on treatment outcomes with basal-bolus insulin regimens in patients with diabetes who have undergone renal transplantation [21]. We observed significant reductions in mean HbA1c from 8.9% to 7.2%, FPG from 237.9 mg/dL to 122.3 mg/dL, and PPG from 342.2 mg/dL to 173.0 mg/dL (all p < 0.001; Table *2*). Fifty-one (45.54%) patients achieved HbA1c ⩽7%, while 52 (46.43%) had HbA1c >7% and <8%. Serum creatinine decreased, and eGFR increased during follow-up (Table *2*). The observed reduction in serum creatinine and increase in eGFR during follow-up may reflect post-transplant recovery of renal allograft function rather than an effect of insulin therapy. Given the retrospective observational design, these changes cannot be attributed to the insulin regimens evaluated. There was a significant but modest mean weight gain of 1.24 kg associated with basal-bolus insulin therapy (p < 0.001; Table *2*). Similar improvements in glycemic parameters from baseline to week 24 were also observed in the degludec and glargine groups (Tables *3*-*4*).

In a previous study by Garber et al. involving patients with advanced, insulin-treated T2DM, reductions in HbA1c, FPG, and PPG with a degludec-based basal-bolus insulin regimen were noninferior to those with a glargine-based regimen, as expected from the treat-to-target trial design [22]. In the present study, there were no significant differences in baseline or week 24 HbA1c, FPG, or PPG between the basal insulin groups (degludec vs. glargine) (Table *5*). Early post-transplant hyperglycemia has been associated with overall long-term graft loss in renal transplant recipients [23]. In our study, significant reductions in FPG were observed with both insulin degludec and glargine (Tables *3*-*4*).

These findings are consistent with the BEGIN Basal-Bolus trial by Garber et al., which also demonstrated comparable glycemic efficacy of degludec and glargine in patients with long-standing T2DM [22]. However, unlike the BEGIN trial, our study specifically evaluated renal transplant recipients, a population with rapidly changing insulin requirements due to fluctuating renal function and immunosuppressive therapy.

Insulin degludec has been associated with weight gain during treatment in previous studies [22]. In our study, weight gain was numerically greater in the glargine group than in the degludec group (1.45 vs. 1.07 kg). The between-group difference was not statistically significant using Welch's independent-samples t-test (p = 0.061), although the Mann-Whitney U test indicated a statistically significant difference (p = 0.045). Given these discordant findings, the difference in weight gain between the groups should be interpreted cautiously. Garber et al. reported similar mean weight gain at the end of the trial in both groups (3.6 kg (SD 4.9 kg) with insulin degludec and 4.0 kg (SD 4.6 kg) with insulin glargine), though numerically higher with glargine [22]. Although weight gain occurred with both basal insulin analogs, the absolute weight gain in our study was modest (approximately 1.2 kg over 24 weeks), which is substantially lower than that reported in the BEGIN trial. This difference may reflect the relatively short follow-up period and close outpatient monitoring after renal transplantation.

We found no statistically significant differences in the proportions of patients experiencing overall, daytime, or nocturnal hypoglycemia between basal insulin groups (degludec vs. glargine) (Table 6). The wide CIs around the hypoglycemia odds ratios reflect the small number of affected patients and limited statistical power, precluding definitive conclusions regarding differences in hypoglycemia risk between the two insulin groups. Nocturnal hypoglycemia occurred in four of 60 (6.7%) patients in the degludec group and seven of 52 (13.5%) patients in the glargine group (Fisher's exact p = 0.341). There was one episode of severe hypoglycemia in the glargine group. In the treat-to-target study by Garber et al., similar proportions of participants experienced confirmed hypoglycemic events with insulin degludec or glargine; however, rates of nocturnal, overall, and diurnal confirmed hypoglycemia were significantly lower with degludec than with glargine [22]. Many of their documented hypoglycemic episodes were detected incidentally by protocol-specified monitoring, while others were prompted by hypoglycemic symptoms. In our retrospective study, confirmed hypoglycemia included documented symptomatic or asymptomatic episodes with a blood glucose value of ⩽70 mg/dL, as well as severe hypoglycemic events. Hypoglycemic symptoms alone are unreliable for quantifying hypoglycemia because symptoms may develop at variable blood glucose concentrations [24].

The numerically lower incidence of nocturnal hypoglycemia observed with degludec in our study is consistent with findings from randomized controlled trials and meta-analyses [25-27]; however, the between-group difference was not statistically significant (6.7% vs. 13.5%; p = 0.341; Table 6). Thus, our findings do not establish a benefit of degludec over glargine in reducing nocturnal hypoglycemia in renal transplant recipients.

The improvement in renal function observed during follow-up was likely multifactorial and may have reflected recovery after transplantation rather than the direct effects of insulin therapy. Nevertheless, the absence of deterioration in renal parameters during follow-up is reassuring regarding the short-term use of basal-bolus insulin therapy in this population.

The absence of significant differences between regular human insulin and insulin aspart suggests that both approaches can achieve satisfactory short-term glycemic control. This finding is particularly relevant in resource-limited settings where the lower cost of regular human insulin may improve treatment accessibility [28].

Although tacrolimus is known to have diabetogenic effects [29], its relationship with glycemic outcomes in our cohort was inconsistent. The observed association with HbA1c change warrants cautious interpretation, particularly given the potential influence of immunosuppressant dose adjustments, changing renal function, and other factors affecting glycemic control after transplantation. Across categories of HbA1c at the end of the study (HbA1c ⩾8%, >7% to <8%, and ⩽7%), there was no significant difference in the distribution of diabetes duration (p = 0.773). Similar short-term efficacy of regular human insulin and insulin aspart is reassuring and may be particularly relevant in populations with substantial out-of-pocket treatment expenditure.

This study was conducted at a single institution, with consecutive rather than random patient selection and a follow-up period limited to 24 weeks. The causal effects of risk factors on graft function could not be assessed. However, given the limited data on treatment outcomes with basal-bolus regimens in patients with diabetes who underwent renal transplantation, this study provides information on their short-term use in this population. Further studies, ideally randomized controlled trials, are needed to establish the optimum regimens for similar patients. There is limited evidence for the use of insulin degludec in post-transplant patients [21]. Our study provides evidence regarding short-term glycemic control and safety with insulin degludec in patients with diabetes who underwent renal transplantation. We did not assess the impact of comorbidities, pre-transplant treatment, or glycemic control on post-transplant glycemic responses with insulin degludec. Hypoglycemia assessment was limited to events documented in the available clinical records. As the total number of episodes per patient was not available, hypoglycemia event rates per patient-year could not be calculated, and the findings are presented as the number and proportion of patients with documented hypoglycemia. Given the retrospective design and absence of a control group, the observed improvements in glycemic control cannot be attributed exclusively to insulin therapy, as steroid tapering, recovery of renal function, and initially poor glycemic control may also have contributed. The requirement for 24 weeks of available follow-up records may have introduced selection bias, as patients with incomplete follow-up may have been underrepresented.

Furthermore, the nonrandomized selection of basal insulin, influenced by clinical considerations and patient affordability, introduces potential confounding by indication, limiting causal interpretation of comparisons between degludec and glargine. Adjusted comparisons accounting for potential confounders, including pre-transplant glycemic control, renal function, and corticosteroid exposure, could not be performed because the necessary patient-level information was unavailable. Furthermore, the absence of statistically significant differences between the insulin groups should not be interpreted as evidence of equivalent efficacy or safety. Future well-controlled studies with adequate sample sizes will help confirm our findings.

Conclusions

In this 24-week retrospective observational study, basal-bolus insulin therapy was associated with

substantial improvements in glycemic control in renal transplant recipients with pre-existing T2DM, with significant reductions in HbA1c and fasting and postprandial glucose concentrations. Renal function remained stable or improved. Degludec and glargine demonstrated comparable glycemic efficacy, with no statistically significant difference in the proportions of patients experiencing nocturnal hypoglycemia between the two groups. No statistically significant differences in the measured glycemic parameters, renal parameters, or body weight were observed between patients receiving regular human insulin and those receiving insulin aspart. These findings indicate that basal-bolus insulin regimens were associated with improved glycemic control during the early post-transplant outpatient period.

Additional Information

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Narayana Health Rabindranath Tagore International Institute of Cardiac Sciences Ethics Committee issued approval NHRTIICSEC/INV/Non-Reg/2025/005. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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