Original Paper

Investigating the Effects of GLP-1 Agonist (Liraglutide) Treatment on Weight Loss and Metabolic Markers in Obese Kidney Transplant Recipients

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Introduction. This study aimed to evaluate the efficacy and safety of the Glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide in obese kidney transplant recipients (KTRs), with a specific focus on its impact on weight loss, metabolic markers, and tacrolimus levels.
Methods. In a prospective, single-arm study, 33 stable KTRs with a Body Mass Index (BMI) ≥ 30 kg/m² received liraglutide for six months. Anthropometric parameters (weight, BMI), blood pressure, glycemic indices [fasting blood sugar (FBS), Hemoglobin A1c (HbA1c)], lipid profile, renal function markers, and tacrolimus trough levels were measured at baseline, two months, and six months. Data were analyzed using Generalized Estimating Equations (GEE).
Results. Treatment resulted in statistically significant reductions in weight, BMI (-7.91 ± 3.81%), waist circumference, and systolic and diastolic blood pressures ($P < .05$). Significant improvements were also observed in FBS, HbA1c (-5.92 ± 4.81%), lipid profile, serum creatinine, and uric acid. A slight but significant decrease in tacrolimus trough levels occurred (-4.91 ± 9.31%, $P = .006$), without any episodes of acute rejection. Adverse events were primarily mild and gastrointestinal (nausea 15.15%).
Conclusion. Liraglutide may be an effective and relatively safe therapeutic option for inducing weight loss and improving metabolic and hemodynamic parameters in obese KTRs. However, due to the lack of a control group and limited sample size, these findings should be interpreted cautiously and cannot establish causality. Vigilant monitoring of tacrolimus levels remains advisable. Larger, controlled trials are needed to confirm efficacy and safety.

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INTRODUCTION

Kidney transplantation (KT) is the preferred therapeutic option for patients with endstage kidney disease (ESKD). It significantly improves patient survival and quality of life. However, this success has challenges due to the high rates of post-transplant metabolic complications, especially obesity.[1] Obesity is often worsened by long-term use of immunosuppressive drugs, like corticosteroids. It affects more than 30% of kidney transplant recipients (KTRs).[1,2] Obesity contributes to posttransplant diabetes mellitus (PTDM), hypertension, and dyslipidemia, all of which accelerate cardiovascular disease (CVD),

the leading cause of longterm mortality in this population.[2] Additionally, obesity increases the risk of surgical complications, delays in graft function, and may influence long-term allograft survival.[3,4]

Despite the clear need to address post-transplant weight gain, effective and sustainable management strategies are limited. Conventional strategies, including lifestyle modification and exercise, typically produce only modest and shortlived effects in this complex patient group.[3] Although bariatric surgery can be effective, its associated surgical risks and potential hazard for changing the absorption of critical immunosuppressants like tacrolimus make it a less appropriate option for many KTRs.[5] This significant therapeutic gap highlights the urgent need for pharmacological interventions that can provide effective and significant weight loss with metabolic benefits. It is also important that the pharmacological approach maintain a favorable safety profile in immunocompromised transplant recipients.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have recently emerged as a promising therapeutic class. Agents such as liraglutide induce weight loss primarily by delaying gastric emptying and promoting satiety, while also offering direct advantages for glycemic control, blood pressure, and cardiovascular outcomes.[6] This broad range of effects makes GLP-1 RAs especially valuable for managing the complex health risks faced by kidney transplant recipient.[7] However, GLP-1RAs can slow gastric emptying and thereby potentially alter the absorption and efficacy of concomitant oral medications such as tacrolimus. Because tacrolimus has a narrow therapeutic range, caution is required when administering GLP1 RAs after transplantation.[8,9]

Given this scientific rationale, prospective data on the efficacy and, more importantly, the safety of liraglutide in obese, stable KTRs remain limited. Most of the available evidence comes from retrospective analyses or small cohorts of diabetic transplant patients, leaving a significant gap in knowledge. To address this, for the first time in Iran, we conducted a prospective study with two primary objectives. The first was to evaluate the efficacy of liraglutide in promoting weight loss and improving key metabolic and hemodynamic parameters including Body Mass Index (BMI), Hemoglobin A1c (HbA1c), lipid profile, and blood pressure over a six-month period. The second was to carefully assess its safety profile, with particular focus on the impact of liraglutide treatment on tacrolimus trough levels and overall allograft function. This study aims to provide essential evidence to support the safe and effective integration of GLP-1 RA therapy into the clinical management of obese kidney transplant recipients.

MATHERIALS AND METHODS

A longitudinal study was conducted over six months at the kidney transplantation clinic of Labbafi Nejad Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Eligible participants were adults > 18 years who had underwent a kidney transplantation at least six months earlier, attended the endocrinology clinic of Labbafi Nejad Hospital, and were visited by an endocrinologist in order to assess the requirement of GLP-1 RA therapy. All patients provided written informed consent. The study protocol received approval from the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1404.390).

Inclusion Criteria

- Age ≥18 years
- Kidney transplantation performed at least six months prior (to ensure stable post-transplant course)
- Stable allograft function, defined as no rejection episode and serum creatinine change ≤ 0.3 mg/dL in the last three months preceding enrollment
- Stable maintenance immunosuppressive regimen (no dose changes in calcineurin inhibitors, mycophenolate mofetil, or corticosteroids for at least 4 weeks prior to enrollment)
- Stable trough levels of calcineurin inhibitors within the therapeutic range (tacrolimus 5–10 ng/mL or cyclosporine 100–200 ng/mL) at screening
- With or without pre-existing diabetes mellitus (to reflect the real-world KTR population)
- Provision of informed consent and willingness to participate
- BMI ≥30 kg/m²

Exclusion Criteria

- History of pancreatitis
- History of thyroid malignancy (medullary

carcinoma)
- History of gastroparesis
- Pregnancy or lactation
- Multiple endocrine neoplasia (MEN) syndrome

Intervention and Dosing Protocol

All patients received liraglutide (Meltide®, manufactured in Iran) administered as a once-daily subcutaneous injection via a prefilled pen device. The dose was titrated according to a standardized schedule to improve gastrointestinal tolerability: 0.6 mg daily during the first week, increased to 1.2 mg in the second week, 1.8 mg in the third week, and 2.4 mg in the fourth week. From the fifth week onward, patients received the target maintenance dose of 3.0 mg daily, which was continued for the rest of the study period. Medication adherence was assessed based on patient self-reporting at each follow-up visit; however, objective confirmation of compliance through therapeutic drug monitoring was not feasible, as serum liraglutide levels were not measured.

Data collection

Baseline demographic and clinical data were collected at the beginning of the study. Additional clinical parameters including weight, blood pressure, and laboratory indices were assessed at baseline and at two and six months after the initial visit (three time points in total). Adverse events related to liraglutide therapy were documented throughout the study based on patient reports and specialist evaluations. Adverse events included nausea, vomiting, constipation, hypoglycemia, and drowsiness. Hypoglycemia was defined as blood glucose below 70 mg/dl.

Weight was measured to the nearest 0.1 kg using a calibrated Seca scale, with participants barefoot and in light clothing. Height was measured using a non-elastic tape with an accuracy of 0.5 cm, and BMI was calculated using the formula: BMI = weight (kg) / height (m^2). Blood pressure, including both systolic and diastolic values, was assessed using a mercury sphygmomanometer with an appropriately sized cuff. Participants rested for 10 minutes before measurement and reported recent smoking, physical activity, or caffeine intake. Blood pressure was measured twice at intervals of at least 30 minutes, and the mean of the two readings was recorded for analysis.

Serum creatinine, uric acid, glycemic indices including fasting blood sugar (FBS) and HbA1c, and lipid profile (triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) were measured using commercial kits and enzymatic colorimetric methods with photometry. Tacrolimus concentrations were measured using high-performance liquid chromatography (HPLC) at baseline, two- and six-months post-intervention. Venous blood samples, usually from the antecubital vein, were collected at baseline and at two and six months after treatment initiation. Samples were obtained in the seated position following 12–14 hours of fasting. Serum was separated by centrifugation at 3000 rpm for 15 minutes.

Statistical Analysis

Quantitative data were described using mean and standard deviation, and qualitative data were presented as frequency and percentage. The percent change for each parameter for everyone was calculated as follows:

Percent change = [(6-month value − baseline value) / baseline value] × 100.

The mean percentage change along with its standard deviation and 95% confidence interval for all participants was then reported. Finally, a linear Generalized Estimating Equations (GEE) regression test was used to examine the trend of repeated quantitative variables over time (across three time points). In addition, ordinal GEE was used to examine the trend of eGFR as an ordinal variable over time. The correlation structure in the GEE models was specified as exchangeable. All analyses were performed at a significant level of $P < .05$ using STATA version 17 (StataCorp LLC, College Station, TX 77845, USA).

A post-hoc power analysis was performed for the primary outcome, defined as the change in body weight from baseline to 6 months. The mean change was –7.75 kg (SD: 3.79). With a sample size of 33 participants, a two-sided alpha of 0.05, and an effect size (Cohen's d) of 2.04, the achieved power exceeded 99%, indicating that the study was adequately powered to detect the observed effect on weight loss. Additionally, the use of three repeated measurements analyzed with a generalized estimating equation (GEE) model likely contributed to greater precision and increased statistical power for the primary analysis.

RESULTS

Baseline Characteristics

There were 33 obese KTRs in this study, with a mean age of 52.28 ± 11.30 years, ranging from 28 to 73 years. Of these, 18 (54.55%) were male. The average interval after transplantation was 9.15 ± 5.31 years. The mean height of the patients was 167.27 ± 8.77 cm and a mean baseline body weight were 98.60 ± 14.58 kg, so that the baseline BMI was 35.23 ± 4.73 kg/m². Diabetes mellitus and hypertension were the most common comorbidities in patients, occurring in 16 patients (48.48%) each. Alport's syndrome (9.09%), systemic lupus erythematosus (12.12%), hyperlipidemia (15.15%), and Autosomal Dominant Polycystic Kidney Disease (ADPKD, 21.21%) were other significant underlying diseases. Diabetes and hypertension were the most common causes of ESKD that resulted in transplantation, accounting for 30.30% and 27.27% of cases, respectively. The immunosuppressive treatment regimen of all patients (100%) comprises calcineurin inhibitors (CNI) and mycophenolate mofetil (Cellcept). The CNI regimen included, 18.18% of patients (n = 6) receiving cyclosporine and 82.81% (n = 27) using tacrolimus. Additionally, most of the patients were on lipid-lowering medication (96.97%), corticosteroids (96.97%), and antihypertensive medications (93.94%). Among anti-diabetic drugs, 36.36% (n = 12) were on oral medications and 12.12% (n = 4) on insulin at baseline. More detailed information is presented in Table 1.

Table 1. Description of kidney transplant recipients' characteristics

Factors	Values (n = 33)
Age (years, mean ± SD)	52.28 ± 11.30
Gender (n, %)	
Female	15 (45.45)
Male	18 (54.55)
Initial weight (kg)	98.60 ± 14.58
Height (cm)	167.27 ± 8.77
Initial Body Mass Index (BMI, kg/m²)	35.23 ± 4.73
Positive history of: (n, %)	
Diabetes	16 (48.48)
Hyperlipidemia	5 (15.15)
Hypertension	16 (48.48)
Systemic lupus erythematosus (SLE)	4 (12.12)
Alport's syndrome	3 (9.09)
Autosomal Dominant Polycystic Kidney Disease (ADPKD)	7 (21.21)
Cause of kidney transplant (n, %)	
Diabetes	10 (30.30)
Hypertension	9 (27.27)
Systemic lupus erythematosus (SLE)	4 (12.12)
Alport's syndrome	3 (9.09)
Autosomal Dominant Polycystic Kidney Disease (ADPKD)	7 (21.21)
Years since the kidney transplant (mean ± SD)	9.15 ± 5.31
Drug history (n, %)	
Cellcept	33 (100)
Calcineurin Inhibitors (CNIs)	33 (100)
Tacrolimus (TAC)	27 (81.82)
Cyclosporine	6 (18.18)
Corticosteroid	32 (96.97)
Anti-diabetic oral agents	12 (36.36)
Insulin	4 (12.12)
Anti-hypertensive agents	31 (93.94)
Lipid lowering agents	32 (96.97)

Data presented as mean and standard deviation (SD) or frequency (n) and percentages (%)

Efficacy Outcomes

Across the six-month treatment period with liraglutide, anthropometric measures showed consistent and significant reduction. The mean body weight reduced dramatically from a baseline of 98.60 ± 14.58 kg to 90.84 ± 14.23 kg after six months, as shown in Table 2, with a mean percent reduction of -7.91 ± 3.81% ($P < .001$). The BMI decreased from 35.23 ± 4.73 kg/m² to 32.46 ± 4.65 kg/m², reflecting the same percent drop of -7.91 ± 3.81% ($P < .001$). Significant decreases in central adiposity markers were also noted. Hip circumference reduced from 118.40 ± 9.30 cm to 113.45 ± 9.27 cm (-4.18 ± 2.01%, $P < .001$) and waist circumference from 111.64 ± 10.48 cm to 106.03 ± 10.03 cm (-5.01 ± 1.97%, $P < .001$). The waist-to-hip ratio also showed a declining trend, although it was not statistically significant ($P = .138$). Moreover, systolic blood pressure decreased from 127.86 ± 11.37 mmHg to 122.97 ± 9.66 mmHg (-3.60 ± 5.45%, $P < .001$), while diastolic blood pressure decreased from 80.13 ± 7.96 mmHg to 77.94 ± 7.14 mmHg (-2.47 ± 6.28%, $P = .011$). More detailed information is presented in Table 2.

Additionally, metabolic indices also improved significantly during therapy. FBS decreased from 125.32 ± 38.55 mg/dL to 110.55 ± 30.81 mg/dL (-8.83 ± 19.61%, $P = .009$), representing a significant improvement in glycemic management. The levels of HbA1c reduced from 6.28 ± 0.94% to 5.89 ± 0.84%, with a mean percent reduction of -5.92 ± 4.81% ($P < .001$). Positive changes were seen in the lipid profile including a decline in LDL from 107.67 ± 34.52 mg/dL to 91.08 ± 28.28 mg/dL

Table 2. Changes in anthropometric indices and blood pressure before and after taking the GLP-1 agonist (Liraglutide) among kidney transplant recipients

Parameters	Baseline (T0) Mean ± SD (95% CI)	2 months later (T1) Mean ± SD (95% CI)	6 months later (T2) Mean ± SD (95% CI)	Mean percent changes (%) Mean ± SD (95% CI)	*P*_value time effect	*P*_value time group comparison
Anthropometric assessment						
Weight (kg)	98.60 ± 14.58 (93.42 , 103.76)	95.24 ± 14.21 (90.20 , 100.28)	90.84 ± 14.23 (85.79 , 95.88)	-7.91 ± 3.81 (-9.26, -6.55)	< .001*	T0/T1* T0/T2* T1/T2*
Body Mass Index (kg/m^2)	35.23 ± 4.73 (33.55 , 36.91)	34.04 ± 4.62 (32.40 , 35.68)	32.46 ± 4.65 (30.81 , 34.11)	-7.91 ± 3.81 (-9.26, -6.55)	< .001*	T0/T1* T0/T2* T1/T2*
Waist circumference (cm)	111.64 ± 10.48 (107.92, 115.35)	108.87 ± 10.32 (105.21, 112.54)	106.03 ± 10.03 (102.47 , 109.58)	-5.009 ± 1.97 (-5.71, -4.30)	< .001*	T0/T1* T0/T2* T1/T2*
Hip circumference (cm)	118.40 ± 9.30 (115.10 , 121.70)	115.91 ± 9.24 (112.64 , 119.19)	113.45 ± 9.27 (110.16, 116.74)	-4.18 ± 2.007 (-4.89, -3.46)	< .001*	T0/T1* T0/T2* T1/T2*
Waist to hip ratio	0.94 ± 0.08 (0.91, 0.97)	0.94 ± 0.08 (0.91, 0.97)	0.93 ± 0.07 (0.90, 0.96)	-0.82 ± 3.09 (-1.91, 0.27)	.138	Non-significant
Hemodynamic assessment						
Systolic blood pressure (mmHg)	127.86 ± 11.37 (123.82, 131.89)	125.35 ± 11.03 (121.44, 129.26)	122.97 ± 9.66 (119.54, 126.40)	-3.60 ± 5.45 (-5.53, -1.67)	< .001*	T0/T2*
Diastolic blood pressure (mmHg)	80.13 ± 7.96 (77.31, 82.95)	80.12 ± 7.37 (77.51, 82.74)	77.94 ± 7.14 (75.41, 80.48)	-2.47 ± 6.28 (-4.70, -0.24)	.011*	T0/T2* T1/T2*

*Statistically significant, *P*_value < .05 based on linear Generalized Estimating Equations (GEE)
Percent change = [(6-month value – baseline value) / baseline value] × 100
Data presented as mean ± standard deviation (SD) and 95% confidence interval (95%CI)

(-13.07 ± 18.42%, *P* < .001), reducing total cholesterol from 207.51 ± 62.77 mg/dL to 176.40 ± 49.16 mg/dL (-13.67 ± 10.80%, *P* < .001).

Additionally, there was a minor but significant reduction in HDL cholesterol (-4.74 ± 19.32%, *P* = .037). Meaningfully, renal function indicators demonstrated significant improvement over the study period, as between months two and six, serum creatinine levels significantly decreased, changing from 1.24 ± 0.26 mg/dL to 1.19 ± 0.23 mg/dL (-2.83 ± 13.50%, *P* = .013). In a similar manner, serum uric acid decreased from 5.43 ± 1.23 mg/dL to 4.98 ± 0.78 mg/dL which was also statistically meaningful (-6.10 ± 14.65%, *P* = .005). Over the 6-month treatment period, mean eGFR significantly improved (*P* = .016), with a mean percent increase of 23.56 ± 6.45% from baseline. While there was an apparent improvement in the overall CKD stage at the end of the study, this shift was not statistically significant (*P* = .605). More details are available at Table 3.

Safety and Immunosuppressive Drug Monitoring

The interaction between liraglutide and CNIs was a critical aspect of safety evaluation while using the liraglutide. Tacrolimus trough levels decreased slightly, from 6.95 ± 1.13 ng/mL at baseline to 6.53 ± 0.97 ng/mL at six months as it was statistically significantly, resulting in a mean percent change of -4.91 ± 9.31% (*P* = .006). On the other hand, cyclosporine levels, showed an elevated trend which was not statistically significant (*P* = .472).

As detailed in Table 4, the oral anti-diabetic medication doses were successfully lowered in 50% of users (6/12 patients) and insulin doses in 100% of users (4/4 patients). The dosages of antihypertensives, lipid-lowering drugs, and immunosuppressive drugs (CNIs, corticosteroids, Cellcept) did not change for most patients during the course of the study. Additionally, liraglutide showed a good tolerance profile. The majority of adverse effects were moderate demonstrating gastrointestinal symptoms; five individuals (15.15%) reported temporary nausea as the most frequent symptom. Two individuals (6.06%) had hypoglycemia, and there were no reports of sleepiness. None of patients were excluded from the study due to adverse effects. Importantly, no

Table 3. Changes in laboratory parameters before and after taking the GLP-1 agonist (Liraglutide) among kidney transplant recipients

Parameters	Baseline (T0) Mean ± SD (95% CI)	2 months later (T1) Mean ± SD (95% CI)	6 months later (T2) Mean ± SD (95% CI)	Mean percent changes (%) Mean ± SD (95% CI)	*P*_value time effect	*P*_value time group comparison
Serum factors						
Fasting blood sugar (FBS, mg/dl)	125.32 ± 38.55 (111.65, 138.99)	116.01 ± 34.69 (103.71, 128.31)	110.55 ± 30.81 (99.63, 121.48)	-8.83 ± 19.61 (-15.78, -1.87)	.009*	T0/T1* T0/T2* T1/T2*
HbA1c (%)	6.28 ± 0.94 (5.94, 6.62)	6.02 ± 0.89 (5.71, 6.34)	5.89 ± 0.84 (5.59, 6.19)	-5.92 ± 4.81 (-7.63, -4.21)	< .001*	T0/T1* T0/T2* T1/T2*
Total cholesterol (mg/dl)	207.51 ± 62.77 (208.17, 235.15)	188.44 ± 56.51 (195.82, 219.53)	176.40 ± 49.16 (182.20, 204.58)	-13.67 ± 10.80 (-14.73, -9.84)	< .001*	T0/T1* T0/T2* T1/T2*
HDL (mg/dl)	72.48 ± 17.78 (66.18, 78.79)	69.48 ± 14.27 (64.42, 74.54)	67.02 ± 14.66 (61.82, 72.22)	-4.74 ± 19.32 (-11.59, 2.10)	.037*	T0/T2*
LDL (mg/dl)	107.67 ± 34.52 (95.43, 119.91)	100.50 ± 27.14 (90.88, 110.13)	91.08 ± 28.28 (81.05, 101.11)	-13.07 ± 18.42 (-19.60, -6.53)	< .001*	T0/T1* T0/T2* T1/T2*
Triglyceride (mg/dl)	207.51 ± 62.77 (185.25, 229.77)	188.44 ± 56.51 (168.40, 208.48)	176.40 ± 49.16 (158.97, 193.83)	-13.67 ± 10.80 (-17.50, -9.84)	< .001*	T0/T1* T0/T2* T1/T2*
Creatinine (mg/dl)	1.24 ± 0.26 (1.15, 1.34)	1.28 ± 0.24 (1.20, 1.37)	1.19 ± 0.23 (1.11, 1.28)	-2.83 ± 13.50 (-7.62, 1.94)	.013*	T1/T2*
Uric acid (mg/dl)	5.43 ± 1.23 (5.002, 5.87)	5.14 ± 1.02 (4.77, 5.50)	4.98 ± 0.78 (4.70, 5.26)	-6.10 ± 14.65 (-11.30, -0.90)	.005*	T0/T1* T0/T2*
eGFR (ml/min/1.73m^2)	65.11 ± 19.46 (58.21, 72.01)	61.95 ± 16.94 (55.94, 67.96)	67.71 ± 19.58 (60.76, 74.66)	6.45 ± 23.56 (-2.54, 15.44)	.016*	T1/T2*
eGFR levels (n, %)						
≥ 90	4 (12.12)	2 (6.06)	5 (15.15)	-	.605	Non-significant
60 – 89	13 (39.39)	16 (48.48)	14 (42.42)	-		
30 – 59	16 (48.48)	15 (45.45)	14 (42.42)	-		
< 30	0 (0.0)	0 (0.0)	0 (0.0)	-		
Serum Calcineurin Inhibitors (CNIs) levels						
Tacrolimus (TAC, ng/ml)	6.95 ± 1.13 (6.50, 7.41)	6.95 ± 0.96 (6.29, 7.05)	6.53 ± 0.97 (6.11, 6.96)	-4.91 ± 9.31 (-9.04, -0.78)	.006*	T0/T2*
Cyclosporine (ng/ml)	137.67 ± 45.18 (90.24, 185.08)	143.50 ± 58.30 (82.31, 204.68)	147.0 ± 60.70 (83.29, 210.70)	5.98 ± 13.75 (-8.44, 20.41)	.472	Non-significant

eGFR: estimated Glomerular Filtration Rate based on CKD-EPI-2021
Percent change = [(6-month value – baseline value) / baseline value] × 100
Data presented as mean ± standard deviation (SD) and 95% confidence interval (95%CI) or frequency and percentages
*Statistically significant, P_value < .05 based on linear Generalized Estimating Equations (GEE)

Table 4. Changes in medication regimen and occurrence of adverse drug events during 6 months after taking the GLP-1 agonist (Liraglutide) among kidney transplant recipients

Medication regimen	Frequency (%)
Cellcept (n = 33)	
Dose reduction	1 (3.03)
No change	32 (96.97)
Increased dose	0 (0)
Calcineurin Inhibitors (CNIs) (n = 33)	
Dose reduction	0 (0)
No change	33 (100)
Increased dose	0 (0)
Corticosteroid (n = 32)	
Dose reduction	0 (0)
No change	32 (100)
Increased dose	0 (0)
Anti-diabetic oral agents (n = 12)	
Dose reduction	6 (50.0)
No change	6 (50.0)
Increased dose	0 (0)
Insulin (n = 4)	
Dose reduction	4 (100)
No change	0 (0)
Increased dose	0 (0)
Anti-hypertensive agents (n = 31)	
Dose reduction	0 (0)
No change	31 (100)
Increased dose	0 (0)
Lipid lowering agents (n = 32)	
Dose reduction	0 (0)
No change	32 (100)
Increased dose	0 (0)
Adverse drug events (ADEs)	
Hypoglycemia (Yes)	2 (6.06)
Nausea (Yes)	5 (15.15)
Drowsiness (Yes)	0 (0)

Data presented as frequency (n) and percentages (%)

significant side effects required discontinuation of liraglutide treatment.

DISCUSSION

The introduction of GLP1 RAs has changed the management of type 2 diabetes and obesity, making their potential application in KTR an important area of ongoing research.[2,10] The KTR population is at high risk for PTDM and obesity, and has a significant increased risk of cardiovascular disease, which is the leading cause of death in these patients.[10] This study, conducted for the first time in Iran, demonstrated that liraglutide may be an effective and relatively safe option for managing obesity and metabolic syndrome in stable KTRs.

The efficacy of GLP-1 RAs in promoting weight loss and improving glycemic control is well-established in the general population and is an important reason for their use in KTRs.[10] Furthermore, our finding of an 8% reduction in BMI over six months is a clinically significant outcome. It aligns with other studies in transplant recipients, although the scale of the effect varies. For instance, Alamo *et al.* demonstrated that, of 52 KTRs treated with GLP-1 RAs, an average weight loss of 4.3 kg over 12 months were observed.[11] Moreover, a meta-analysis that included 12 studies on GLP-1 RAs in KTRs also confirmed that using GLP-1 RAs were association with significant weight loss and a reduction of about 0.48% in HbA1c.[12] On the other hand, in solid organ transplant recipients, a retrospective comparison of dulaglutide and liraglutide revealed that during a 24-month period, dulaglutide demonstrated a 5.2% weight decrease, while liraglutide showed a reduction of less than 1%.[13] In addition, statistically significant improvements in blood sugar control, including the reduction of HbA1c and FBS, could indicate the ability of liraglutide to simplify treatment regimens, including reducing the dose of insulin and oral antidiabetic drugs, as reducing the number of drugs is a key advantage in KTRs as they already facing significant polypharmacy.[14]

GLP1 RAs have previously displayed cardiorenal protective effects in large trials involving nontransplant populations, which provides strong justification for their use in KTRs. These drugs dramatically lower the risk of major adverse cardiovascular events (MACE), including cardiovascular death, according to important trials like LEADER (liraglutide) and SUSTAIN-6 (semaglutide).[15,16] The LEADER trial discovered that liraglutide compared to the placebo can reduce the risk of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke about 13%.[16] More recently, the FLOW trial, which focused on patients with type 2 diabetes and chronic kidney disease, demonstrated 24% reduction in the risk of major kidney disease events and death from cardiovascular or kidney-related causes.[17]

However, before attributing these metabolic improvements solely to liraglutide, the potential confounding effect of concomitant medications must be carefully evaluated. When interpreting the observed improvements in weight and lipid profile, the potential confounding effect of concomitant

medications must be considered. We observed that the majority of immunosuppressive and metabolic agents remained at stable doses throughout the 6month followup period. Notably, corticosteroids, calcineurin inhibitors, antihypertensive drugs, and lipidlowering agents were maintained without any dose adjustment in all patients. This stability strongly argues against these medication classes being major confounders for the weight loss and lipid improvements observed in our cohort. The only dose modifications were reductions in oral antidiabetic agents (in 50% of patients) and insulin (in 100% of patients), which were expected consequences of the glucoselowering effect of liraglutide rather than independent external confounders. Therefore, while we acknowledge that residual confounding from unmeasured variables cannot be entirely excluded, our data do not support a significant role for concomitant medication changes in driving the metabolic benefits observed. Nevertheless, the lack of detailed dietary and physical activity records remains a limitation, and future studies with stricter control of these variables are warranted.

Our findings indicate that stable allograft function during liraglutide therapy, with significant decreases in serum creatinine (P = .013) and uric acid (P = .005), suggesting a favorable trend in kidney function. However, these observed decreases—particularly in creatinine—cannot be entirely attributed to a direct reno-protective action of liraglutide given the limitations inherent in our study design, and thus our interpretation must remain cautious. Nevertheless, these results are consistent with a growing body of evidence, such as the work by Greco and Yu, which proposes multiple pathways through which GLP-1 RAs may exert renal effects.[18,19] These mechanisms are likely multifactorial, potentially encompassing both direct renal actions and indirect hemodynamic improvements.[20] The latter could be partially explained by the well-established effects of GLP-1 RAs on reducing blood pressure and weight, which may collectively decrease the hemodynamic load on the kidney graft.[10,21] Furthermore, the natriuretic properties of these agents, which promote sodium excretion and reduce fluid retention, may also contribute to blood pressure regulation.[22,23] These findings align with data from large-scale cardiovascular outcome trials in non-transplant populations, such as LEADER and SUSTAIN-6, which reported reductions in new or worsening nephropathy.[15,16] While this consistency is encouraging, we acknowledge that the short followup period in our study precludes any inference regarding longterm reno-protective outcomes, particularly graft survival, in kidney transplant recipients. Therefore, our interpretation remains hypothesisgenerating and underscores the need for further dedicated longterm studies in this specific population.[10]

Hence, the stability of allograft seen in the study shows important clinical evidence that these well-established reno-protective mechanisms may also be helpful in the post-transplant setting, which offer a treatment option that simultaneously addresses metabolic health and the maintenance of important graft function. On the other hand, although GLP-1 RA therapy improved KTRs outcome, Alamo *et al.* demonstrated that the favorable effects on proteinuria were less pronounced than in a matched group of patients with chronic kidney disease, potentially because of the confounding effects of immunosuppressants.[11]

The safety of liraglutide is an important consideration in this vulnerable population, which requires special attention to drug side effects and risks associated with immunosuppressive drugs. Our study showed that liraglutide was generally well tolerated over the sixmonth treatment period. The most commonly reported side effects, which were transient in nature, included nausea (15.15%) and, to a lesser extent, mild hypoglycemia (6.06%). Krisanapan *et al.* reported that the incidence of gastrointestinal side effects is comparable to that reported in general trials.[1] More importantly, no cases of acute allograft rejection, pancreatitis, or other serious drug-related adverse events necessitating treatment discontinuation were observed during this study. This safety profile suggests liraglutide as a possible treatment option in the KTRs population. Schmitz *et al.* demonstrated that although these side effects are frequent, they are usually mild to moderate, manageable with proper dose titration and patient counseling, and rarely result in discontinuation of treatment.[10] Fortunately, there is currently no evidence that KTRs receiving these drugs have a higher risk of pancreatitis or acute allograft rejection.[10,12] Although a solitary fatal case of necrotizing pancreatitis in a KTR was

reported in Alamo *et al.* study, the treatment was generally considered well-tolerated.[11]

The findings highlight a clinically relevant interaction between liraglutide and tacrolimus. Tacrolimus trough levels showed a modest but significant decline (-4.91%, $P = .006$), likely due to delayed gastric emptying affecting drug absorption.[24] In contrast, cyclosporine levels showed a nonsignificant upward trend ($P = .472$); however, this finding should be interpreted cautiously given the small sample size (n = 6) and its higher pharmacokinetic variability.[10,14] Importantly, no acute rejection episodes occurred, and no CNI dose adjustments were required in any patient during the 6month followup. This observation, alongside the stable allograft function, supports the clinical safety of liraglutide when accompanied by appropriate therapeutic drug monitoring, particularly upon treatment initiation and dose escalation. Moreover, even though a clinically meaningful interaction might not occur frequently, the possible risk demands for a cautious approach, with careful therapeutic medication monitoring of tacrolimus levels, particularly upon beginning and dose escalation of a GLP-1 RA.[10]

Limitation of the study

The present study has limitations that should be considered when interpreting the results. Beyond the limited sample size (N = 33) and short sixmonth followup, the singlearm, uncontrolled design without a concurrent control group substantially restricts our ability to attribute the observed improvements causally to liraglutide. Another limitation of our study is the lack of available data on proteinuria which precludes a more comprehensive assessment of the renal effects of the intervention. These factors collectively reduce the generalizability of the findings and preclude definitive conclusions about longterm graft or patient outcomes. Therefore, studies with larger sample sizes and longer follow-up durations are essential and should be prioritized in future research in this field.

CONCLUSION

In conclusion, while our findings suggest that liraglutide may be a promising therapeutic option for obese KTRs, yielding clinically meaningful improvements in weight, metabolic parameters, and blood pressure with an acceptable shortterm safety profile, the inherent limitations of the study design preclude definitive causal claims. The observed reductions in weight and metabolic markers, alongside stable graft function and no rejection episodes, are encouraging but require confirmation in wellpowered, randomized controlled trials with longer observation periods before liraglutide can be routinely recommended for this indication.

DECLARATIONS

Competing interests

Authors declare that there was no any conflict of interest.

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