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ORIGINAL PAPER

Glucagon-like Peptide-1 Receptor Agonists in Kidney Transplant Recipients – A Retrospective Single Center Study

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ABSTRACT

Objetives: The incidence of posttransplant diabetes and the elevated cardiovascular (CV) risk among transplant recipients are on the rise. Glucagon-like peptide agonists have the potential to mitigate the effects of immunosuppressive drugs, addressing both hyperglycemia and weight gain. This makes them appealing for use in this population, given their CV and renoprotective benefits. Nevertheless, there is insufficient substantial evidence regarding their efficacy in diabetic kidney transplant recipients (KTR). **Methods:** The objective of this retrospective study was to assess the effectiveness and safety of glucagon-like peptide agonists in KTR. The primary focus was to evaluate their impact on various parameters, such as hemoglobin A_{1c} levels, body mass index (BMI), lipid panel, hemoglobin levels, renal allograft function (estimated glomerular filtration rate [eGFR]), and urinary protein-to-creatinine ratio. **Results:** During a median observation period of 18 months, this investigation included 64 renal transplant patients. Median eGFR at baseline was 61.9 mL/min/1.73 m^2 and remained stable throughout the follow-up. Median HbA_{1c} decreased from 7.5 to 7% (95%CI; $p < 0.002$). A significant improvement in BMI and lipid panel were also observed. We did not observed significant changes regarding median creatinine and urinary protein:creatinine ratio levels. No side effects justified discontinuation of the drug. **Conclusion:** This study shows that the use of glucagon-like peptide agonists is feasible and well-tolerated in KTR, with no significant side effects observed. Subsequent studies are needed to explore whether glucagon-like peptide agonists can effectively improve allograft survival in these patients.

Descriptors: Glucagon-like Peptide-1 Receptor Agonists; Kidney Transplant; Diabetes Mellitus.

Agonistas do Receptor de Peptídeo Semelhante ao Glucagon-1 em Transplantados Renais - Estudo Retrospectivo de um Centro Hospitalar

RESUMO

Objetivos: A incidência de diabetes pós-transplante e o aumento do risco cardiovascular entre os receptores de transplante estão em ascensão. Os agonistas do receptor de peptídeo semelhante ao glucagon têm o potencial de mitigar os efeitos dos medicamentos imunossupressores, abordando tanto a hiperglicemia quanto o aumento de peso, o que os torna atrativos para uso nesta população, dadas as suas vantagens cardiovasculares e renoprotetoras. No entanto, a evidência atual é insuficiente sobre a sua eficácia em receptores de transplante renal diabéticos (RTRD). **Métodos:** O objetivo deste estudo retrospectivo foi avaliar a eficácia e segurança dos agonistas do peptídeo semelhante ao glucagon-1 em RTRD. O foco principal foi avaliar o seu impacto em vários parâmetros, tais como níveis de hemoglobina A1c, índice de massa corporal (IMC), perfil lipídico, níveis de hemoglobina, função do enxerto renal (taxa de filtração glomerular estimada [TFGe]) e relação proteína-creatinina urinária. **Resultados:** Durante um período de observação mediano de 18 meses, esta investigação incluiu 64 pacientes transplantados renais. A TFGe mediana no início foi de 61,9 mL/min/1,73 m2 e permaneceu estável durante o acompanhamento. A mediana da HbA1c diminuiu de 7,5 para 7% (IC95%; $p < 0,002$). Também foi observada uma melhoria significativa no IMC e no perfil lipídico. Não foram observadas mudanças significativas nos níveis medianos de creatinina e relação proteína:creatinina urinária. Nenhum efeito colateral justificou a descontinuação do medicamento. **Conclusão:** Este estudo mostra que o uso de agonistas do peptídeo semelhante ao glucagon é viável e bem tolerado em RTRD, sem efeitos colaterais significativos observados. Estudos subsequentes são necessários para explorar se esta terapêutica pode melhorar efetivamente a sobrevida do aloenxerto nesses pacientes.

Descritores: Agonistas do Receptor de Peptídeo Semelhante ao Glucagon-1; Transplante Renal; Diabetes Mellitus.

INTRODUCTION

Diabetes mellitus (DM) stands as a primary contributor to atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and end-stage kidney disease (ESKD), and its prevalence continues to rise.[1]

DM also emerges as a prominent comorbidity following solid organ transplantation, imparting long-term detrimental effects on transplant recipients.[2]

Renal transplantation is the preferred treatment for ESKD, providing patients with an enhanced quality of life and lower mortality risk compared to dialysis. For kidney transplant recipients (KTR), DM remains a substantial burden, with nearly 40% of individuals carrying a pretransplant diagnosis of diabetes, primarily type 2 DM (T2DM). Additionally, 10-20% of recipients without preexisting DM develop posttransplant DM (PTDM). Both preexisting T2DM and PTDM exert adverse effects on both patient and kidney allograft outcomes, increasing the risk of rejection, infection, diabetes-related microvascular and macrovascular complications and, ultimately, graft loss with consequently diminished survival rates.[3]

Importantly, KTR with diabetes confront a 50% elevated risk of graft failure compared to those without diabetes, and almost half of kidney grafts suffer from recurring diabetic kidney disease (DKD). Recognized factors contributing to PTDM include advanced recipient age, receiving a kidney from a deceased donor, administration of calcineurin inhibitors (CNI) and corticosteroids, as well as having adult polycystic kidney disease, alongside conventional risk elements for T2DM. Approaches to manage PTDM involve initiating insulin therapy promptly, implementing lifestyle changes like dietary adjustments and physical activity, considering bariatric surgery, and modifying immunosuppressive regimens to minimize CNI and steroid usage.[3,4]

These results highlight the critical need to address risk factors and explore novel treatments in this patient demographic. Nevertheless, there is a scarcity of data due to the customary exclusion of transplant recipients from clinical trials evaluating innovative therapies.[2]

In the past 5 years, there has been notable advancement in the management of DKD. Glucagon-like peptide-1 receptor agonists (GLP1RA) have become recognized as a beneficial option for reducing the risk of complications related to T2DM in nontransplant patients. Clinical trials have demonstrated improved cardiovascular (CV) and renal outcomes with GLP1RA treatment, including a reduction in the relative risk of myocardial infarction, stroke, and CV death among patients with established ASCVD.[1,4,5]

However, there remains a persistent apprehension regarding the safety and acceptability of these medications in KTR. This concern mainly arises from potential gastrointestinal adverse effects linked to delayed gastric emptying, leading to worries about potential interference with the absorption of medications essential for transplant recipients.[4,5]

Furthermore, addressing posttransplantation diabetes presents distinctive hurdles, including potential drug interactions between antidiabetic and immunosuppressive agents, alongside compromised kidney function. Additionally, concerns about adverse effects such as fluid retention, weight gain, lactic acidosis, delayed gastric emptying, and adverse effects on bone health may affect the overall well-being of KTR. Queries regarding these matters are met with ambiguity due to the scarcity of available literature on the utilization of GLP1RA following kidney transplantation.[4,5]

We aimed to fill this knowledge void by evaluating the outcomes and safety of GLP1RA therapy specifically in KTR with diabetes at our medical centers.

METHODS

We undertook a retrospective study encompassing all adult recipients of kidney transplants who initiated GLP1RA treatment to glycemic control regardless of previous antidiabetic treatment. The research covered a median follow-up duration of 23.5 (ranging from 3.0 to 115.0) months. Eligibility criteria included patients who did not experience acute kidney injury (AKI) within the 30 days prior to starting the medication. Two exclusion criteria were implemented: individuals diagnosed with type 1 diabetes (T1DM) and those undergoing a combined kidney and pancreas transplant.

In our study, we primarily investigated various outcomes, including hemoglobin A_{1c} levels, body mass index (BMI), lipid panel parameters (such as low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglycerides), hemoglobin levels, renal allograft function (estimated glomerular filtration rate [eGFR]), and urinary protein-to-creatinine ratio. These evaluations were performed at both the beginning and the end of the follow-up period. Throughout the study duration, we closely monitored potential complications associated with the use of GLP1RA, and adverse events were minimal, with similar safety observed across all groups.

During their renal transplant consultations, patients received regular follow-ups, and the introduction of GLP1RA was carried out by team members who provided detailed explanations regarding the potential side effects.

Statistical analysis

Demographic, clinical, and laboratory information were collected and analyzed using descriptive statistics with SPSS Statistics software. The data were presented as means ± standard error, and comparisons were made using the analysis of variance (ANOVA) test. Statistical significance was considered at a threshold below 0.05 ($p < 0.05$). We used the Wilcoxon rank sum test to compare quantitative data across groups.

RESULTS

The study encompassed 64 individuals who underwent renal transplantation. One patient was excluded for experiencing AKI within the 30 days prior to starting the medication, two patients with T1DM, and four patients submitted to a double kidney and pancreas transplant. The average age of the participants was 60.1 ± 12.1 years, and 62.5% of them were male. Out of these, 64% were diagnosed with posttransplant diabetes. Most patients had prior exposure to antidiabetic treatments: insulin (54%), metformin (25.1%), and DPP4 inhibitors (14.1%).

The prevalent concurrent conditions included high blood pressure (92.8%), abnormal lipid levels (81.5%), and obesity (BMI > 30) in 13% of the participants. The median period since receiving the transplant was 8.6 years, with 81% having undergone kidney donation from deceased donors and 19% receiving kidneys from living donors. The primary maintenance immunosuppressive regimen consisted mainly of CNI (93%), mycophenolate mofetil (83%), and corticosteroids (90%). The median duration between transplantation and the start of GLP1RA treatment was 8.0 years. The study spanned a median observation period of 20 (4.0-101.0) months. At baseline, the median HbA_{1c} was 7.8% (5.3-16.7%). The characteristics of patients are detailed in Table 1.

Table 1. Baseline characteristics of study patients (mean) (n = 64)

Characteristics	
Age, years	60 (24-81)
Gender, female/male, %	38.0/62.0
Living kidney donation, %	19.0
Maintenance immunosuppression,%	
Calcineurin inhibitors	93.0
Mycophenolate mofetil	83.0
Median HbA_{1c} , %	7.8
Time since transplantation, years	8.6
Posttransplant diabetes mellitus, %	64.0
Underlying chronic disease, %	
Diabetic/hypertensive nephropathy	28.1
IgA nephropathy	6.2
Polycystic kidney disease	10.9
Unknown	28.1
Other	26.7
Previous antidiabetic therapies, %	
Insulin	54.0
DPP4 inhibitors	14.1
Metformin	24.1
SGLT2i	31.1
Comorbid conditions, %	
Hypertension	92.8
Dyslipidemia	81.5
Obesity	13.0

Source: Elaborated by the authors

Notable improvements were observed in HbA_{1c} and BMI, along with enhancements in hemoglobin levels and lipid profiles. The mean change in HbA_{1c} was 0.45% (standard deviation [SD] 1.6, $p = 0.002$), and there was a mean BMI improvement of 0.5 kg/m^2 (SD 4.7, $p = 0.03$). Additionally, there was a statistically significant reduction in lipid panel parameters, including LDL cholesterol (SD 31.0, $p = 0.003$) and total cholesterol (SD 35.0, $p = 0.02$) ($p = 0.05$). The median hemoglobin level at baseline was 13.0 g/dL, which significantly improved to 13.5 g/dL by the end of the follow-up period ($p = 0.002$).

The median estimated creatinine level at baseline was 1.53 and 1.41 mg/dL (SD 0.6, $p = 0.3$) at end of the follow-up. Similarly, the urine protein to creatinine ratio (uPCR) at baseline was 0.57 g/g and 0.43 mg/dL at end of the follow-up (SD 1.3, $p = 0.18$).

The rate of side effects like hypoglycemia or gastrointestinal symptoms was minimal (< 1%), with no report of patients discontinuing the drug. There were no events of pancreatitis reported.

DISCUSSION

Diabetes, affecting 422 million globally and expected to reach 700 million by 2045, mainly presents as T2DM, raising risks of CV diseases (CVD) and chronic kidney diseases (CKD). CKD affects 30-40% of diabetics, often progressing to kidney failure. Shared risk factors with CVD and CKD highlight diabetes' role. Treatment, including GLP1RA and SGLT2i, extends beyond glucose control. Early medication intervention is crucial. Kidney transplantation is preferred for end-stage renal disease, with improved posttransplant life expectancy due to advancements.[6,7]

Transplant recipients often have insulin resistance and impaired insulin secretion, leading to diabetes with a higher risk of atherogenic dyslipidemia, hypertension, and CVD mortality.[7]

New onset diabetes after transplantation (NODAT) prevalence is underestimated due to differing definitions and is associated with poorer graft function and survival posttransplant compared to nondiabetic controls. One-year survival for diabetic transplant patients is 83 vs. 98% without diabetes; 2-year survival is 67 vs. 83%, emphasizing NODAT's impact.[6,8,9]

Impaired graft survival in NODAT patients stems from factors like diabetic nephropathy, uncontrolled hypertension, and lower immunosuppressive dosages. NODAT also incurs high healthcare costs posttransplant.[10]

In summary, NODAT impacts graft outcomes and increases healthcare costs. Identifying at-risk patients is crucial for tailored treatments and preventive measures to manage NODAT and improve long-term outcomes in KTR.[6-10]

The incretin system is key in diabetes management, with intestinal hormones stimulating insulin and suppressing glucagon release, reducing blood glucose levels.[11]

Incretin hormones (gastric inhibitory polypeptide [GIP], glucagon-like peptide-1 [GLP-1]) boost insulin release postoral glucose, reduced in T2DM. GLP1RA mirrors GLP-1, ups insulin, curbs glucagon, and lowers hypoglycemia. Targeting GLP-1 receptors bypasses interactions, enhancing insulin sensitivity, slowing gastric emptying, reducing appetite, and exhibiting anti-atherogenic effects, aiding T2DM management.[12-14]

GLP1RAs exhibit different chemical compositions and pharmacokinetic patterns, categorized primarily as short-acting and long-acting formulations. Both long-acting and short-acting GLP-1 formulations offer various benefits, with short-acting agents having a stronger effect on gastric emptying and postprandial hyperglycemia, while long-acting GLP1RAs primarily focus on reducing fasting blood glucose levels.[15-17]

Exenatide and exenatide extended release, approved by the U.S. Food and Drug Administration (FDA) for T2DM, are eliminated through the kidneys and should be avoided in patients with a creatinine clearance less than 30 mL/min due to the risk of accumulation, leading to nausea, vomiting, and AKI. In contrast, liraglutide and dulaglutide are only degraded by endogenous proteolysis without specific organ involvement, making them suitable for use in advanced CKD and even in ESKD patients with caution.[1-4]

GLP1RA exhibits various beneficial actions, including antidiabetic, antihypertensive, anti-inflammatory, anti-apoptotic, and immunomodulatory effects. The benefits of GLP1RA also extend to improved CV and renal outcomes, with recent meta-analyses showing CV safety, reduced major adverse cardiovascular events (MACE), reduced risk of new-onset albuminuria, decline in estimated glomerular filtration rate (eGFR) and progression to ESKD.[1-4]

Clinical trials commonly categorize kidney endpoints into "cardio-renal" and "renal-specific" outcomes. Cardiorenal outcomes include eGFR reduction, ESKD, renal replacement therapy (RRT), and kidney/CV death; some real-world studies replace CV death with all-cause mortality (ACM). Renal-specific outcomes exclude CV death/ACM, focusing on renal effects. Cardiovascular Outcome Trials (CVOTs) like ELIXA, REWIND, LEADER, SUSTAIN 6, and PIONEER 6 follow diverse T2DM populations, assessing GLP1RA impact on CV/kidney outcomes. Patient inclusion varied; eGFR ranged 75-80 mL/min/1.73 m^2, limiting data on advanced CKD (eGFR < 30 mL/min/1.73 m^2) effects.[18-22]

Most participants in GLP1RA CVOTs had normoalbuminuria at baseline, with around 15% having proteinuria (UACR > 300 mg/dL). Limited baseline kidney disease hindered assessing treatment effects on kidney outcomes within trial durations. Exposure duration to GLP1RAs varied (median 5.4 years in REWIND to 15.9 months in PIONEER 6). Compliance ranged from 76% (EXSCEL) to 86.5% (SUSTAIN 6).[18-22]

In the LEADER trial, liraglutide showed greater reduction in MACE among patients with an eGFR < 60 mL/min. Additionally, liraglutide effectively lowered the incidence of new-onset CKD and decelerated its progression, largely attributed to addressing persistent macroalbuminuria. Importantly, the rate of renal adverse events, including AKI, was comparable between liraglutide and placebo groups in the trial.[18,19] In the REWIND trial involving dulaglutide, there was a decrease in MACE along with a decline in the occurrence of new instances of significantly elevated albuminuria. Additionally, dulaglutide contributed to

the sustained preservation of eGFR and reduced the need for (RRT).[20] In the AWARD 7 trial involving dulaglutide conducted in individuals with moderate-to-severe CKD, it was found that dulaglutide provided comparable glycemic control to insulin while also leading to a reduced decline in eGFR. This trial, which spanned 52 weeks of follow-up, was the first to illustrate that dulaglutide can mitigate the decrease in eGFR when compared to insulin glargine in patients with T2DM and moderate-to-severe CKD.[21] The CV outcomes trial SUSTAIN 6, which evaluated weekly semaglutide, showed that it was safe and led to a significant reduction in MACE.[22]

Kidney outcomes observed in GLP1RAS CVOTs can be broadly divided into two categories: composite outcomes involving changes in albuminuria (specifically the onset of persistent proteinuria with UACR greater than 300 mg/dL) and composite kidney outcomes solely based on eGFR. The ELIXA trial revealed that lixisenatide reduced UACR in patients with macroalbuminuria, but did not affect eGFR. In the LEADER trial, liraglutide decreased the composite kidney outcome, including new-onset persistent macroalbuminuria, doubling of serum creatinine levels, ESKD, or death related to kidney disease. This improvement in kidney outcomes was consistent across different baseline eGFR and UACR subgroups. Furthermore, the LEADER trial suggested potential kidney protection with liraglutide in patients with CKD stage 3. It stands out as the CVOT with GLP1RA providing the most comprehensive data on the impact of GLP1RAS on kidney function. Similarly, in the SUSTAIN 6 trial, the kidney outcomes resembled those of the LEADER trial. Semaglutide reduced the incidence of new or worsening nephropathy compared to placebo, driven by a decrease in persistent macroalbuminuria. The overall decline in eGFR was similar between groups, regardless of baseline kidney function. The initial reduction in eGFR with semaglutide tapered off over time, similar to the initiation of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and sodium-glucose cotransporter 2 inhibitor (SGLT2i). Semaglutide also resulted in greater reductions in UACR, except in cases of normoalbuminuria.[20-22]

In the EXSCEL trial, most laboratory assessments were conducted at local facilities, and the trial protocol did not initially include a predefined composite kidney outcome. However, in a subsequent analysis, a composite kidney outcome was defined as a 40% reduction in eGFR, initiation of RRT, kidney-related death, or new onset macroalbuminuria. Initially, this composite outcome did not show a significant difference between exenatide once-weekly (OW) and placebo. Nevertheless, after adjusting for multiple variables, the adjusted hazard ratio (HR) revealed a borderline significant reduction in risk with exenatide OW compared to placebo. Despite methodological limitations, these findings provide supportive evidence suggesting the kidney safety profile of exenatide OW.[18,19]

Several randomized controlled trials (RCTs), including HARMONY 8, LIRA-RENAL, AWARD-7, and PIONEER, examined GLP1RAs in kidney dysfunction. They varied in baseline eGFR and urinary albumin excretion. Primarily assessing HbA_{1c} change, trials like LIRA-RENAL and PIONEER demonstrated GLP-1 RAs' efficacy, while HARMONY 8 highlighted albiglutide's kidney safety. However, these trials, lasting 26 or 52 weeks, were underpowered to assess hard kidney endpoints, despite showing no detrimental effects on kidney function. PIONEER 5 findings suggested that oral semaglutide might be linked to a decrease in albuminuria.[18-22]

In the AWARD-7 trial, despite achieving similar levels of glycemic control, patients receiving dulaglutide showed a slower decline in eGFR, indicating potential renal protective effects. In the REWIND trial, the composite kidney outcome included the development of new macroalbuminuria, sustained decline in eGFR of ≥ 30%, or chronic RRT. Dulaglutide significantly reduced the incidence of new macroalbuminuria, although reductions in other components were not statistically significant. Sensitivity analyses revealed decreased sustained declines in eGFR of ≥ 40% or ≥ 50% with dulaglutide. UACR was lower in patients treated with dulaglutide, although overall eGFR differences were not significant.[18-22]

Pasternak et al.[23] conducted a study comparing the incidence of serious kidney events in new users of GLP1RA and DPP4i. They found that GLP1RA users had a 24% lower risk (HR 0.76) compared to DPP4i users, with consistent benefits observed across different subgroups. Notably, a greater risk reduction was observed in patients with a history of chronic kidney disease (HR 0.54). These findings were supported by an "on treatment" analysis, despite variations in baseline kidney parameters among the study participants.[23]

GLP1RAs are glucose-lowering agents with benefits also in terms of weight control because they activate the GLP-1 receptor, located on the pancreatic β-cell surface, increasing insulin synthesis and reducing glucagon secretion, food intake, and gastric emptying.[24]

In RCTs involving T2DM participants, GLP1RA reduced hemoglobin A_{1c} by 0.5-1.8%, and some agents led to weight losses of up to 7 kg compared with placebo. Moreover, GLP1RA have profound effects on weight in obesity studies, with a 14.9% greater weight loss described with semaglutide compared to placebo ($p < 0.001$). Obesity is a significant barrier to kidney transplantation in ESKD, underscoring the importance of studying effective obesity therapies. GLP1RA offers an extra advantage of weight loss, making them particularly attractive for PTDM, where weight gain is often observed. Research has demonstrated that GLP-1 infusion lowers glucagon levels while increasing insulin secretion, presenting potential benefits for PTDM management.[25]

In summary, results indicates that GLP1RA improves glycemia, blood pressure control, weight reduction and managing diabetic dyslipidemia. It regulates cholesterol and triglycerides through various mechanisms. Liraglutide, for example, has been reported to decrease lipid profiles and improve leptin and adiponectin levels.[20] These studies also assess surrogate kidney markers, suggesting potential benefits without deleterious effects on kidney function.[26]

In 2023, American Diabetes Association (ADA) recommends metformin as the first-line drug for children, adults, and the elderly. For adults, SGLT2is and GLP1RAs are also recommended, particularly in cases of CVD, HF, and complications related to CKD or high risk. The Kidney Disease Improving Global Outcomes (KDIGO) 2020 guidelines recommend metformin plus SGLT2 inhibitors as initial therapy for treating hyperglycemia in patients with T2DM and DKD. Additional options include any other antihyperglycemic agent, with a preference for GLP1 receptor agonists as preferred adjunctive agents.[20]

So, GLP1RA holds promise for glycemic control in transplant recipients, offering benefits such as improved HbA_{1c}, weight loss, and potential renoprotective effects.

Although limited studies have evaluated GLP1RA in KTR, existing data suggests favorable outcomes.

There are compelling reasons to consider the use of GLP1RA for glycemic control in transplant recipients. Firstly, NODAT is associated with impaired β-cell function and altered glucose-induced glucagon suppression during hyperglycemia. Secondly, research involving insulinoma cells in mice has shown that pancreatic β-cells expressing GLP-1 may be resistant to the toxic effects of immunosuppressive drugs. In particular, the use of exendin-4 has demonstrated potential in reversing the cell-damaging effects induced by drugs like dexamethasone. Moreover, GLP1RA may target the pathogenesis of NODAT. GLP1RA infusion in this population has demonstrated a reduction in fasting plasma glucose, decreased glucagon concentration, and increased insulin secretion during hyperglycemic clamps contributing to improvements regarding glycemic and weight control.[4,27-29]

Retrospective and observational studies on posttransplant recipients with preexisting T2DM or NODAT using GLP-1R (liraglutide or exenatide) have shown improvements in HbA_{1c} and weight loss without significant changes in serum creatinine and tacrolimus levels. In a larger case series involving dulaglutide, recipients experienced reductions in body weight and insulin requirements, suggesting potential benefits for glycemic control.[28]

In a study comprising 12 KTR, use of GLP-1 receptor agonists resulted in decreased fasting plasma glucose levels, lowered glucagon concentration, and enhanced first- and second-phase insulin secretion during a hyperglycemic clamp.[29] A separate small-scale investigation involving five patients who received liraglutide after kidney transplantation revealed enhancements in glycemic management and weight, without any detrimental effects on renal function of the graft following an average follow-up period of 19 months.[4]

In a 2018 study, seven cases with preexisting T2DM or NODAT using liraglutide showed safety and efficacy for glycemic control, with improved graft renal function. In this group, a notable reduction in the median HbA_{1c} of 0.45% was documented. This corresponds with previous findings, which indicate a decrease in HbA_{1c} ranging from 0.8 to 2%. Mahmoud et al.[30] collected 1-year follow-up data from records of 98 diabetic KTRs on SGLT2I, 41 on GLP-1RA and 70 on standard-of-care medicines and showed that HbA_{1c} exhibited a substantial decline of 0.4% in both the SGLT2i and GLP-1RA groups, in contrast to a minimal decrease of 0.05% in the control group. Notably, there was a significant reduction in BMI by 0.32 in the SGLT2i group and 0.34 in the GLP-1RA group, while the control group experienced a slight increase of 0.015. In other retrospective cohort studies in T2DM and kidney transplantation, 12 months of GLP-1RA lowered HbA_{1c} by 2%, and fasting glucose by ~3 mmol/L compared with nonuse, and in some reports, weight losses of up to 4 kg were described.[29,30]

GLP1RA in KTR is justified by their capacity to counteract the impact of immunosuppressive medications on insulin secretion, rendering them potentially advantageous in this scenario. Corticosteroids and CNIs, frequently employed in anti-rejection protocols, influence glucose metabolism, and GLP1RA can mitigate these hyperglycemic effects induced by immunosuppressants.[4,27-29]

Preclinical evidence also suggests potential protective mechanisms for the kidney associated with GLP-1 receptor agonists, such as reductions in protein kinase C signaling, oxidative stress, and inflammatory responses.[1,28,30]

In this group of patients, we observed a substantial and statistically significant ($p < 0.05$) decrease in BMI, lipid levels, and hemoglobin levels at the conclusion of the follow-up period. This indicates that the administration of GLP1RA had a beneficial effect on body weight among KTRs. Indeed, GLP1RA has been showing improvement on lipid profiles and weight loss but up to our knowledge, this is the first study showing favorable results regarding hemoglobin levels.[27-30] The enhancements in lipid profiles linked to GLP1RA contribute to their role in managing CV risk factors, complementing their primary impact on lowering glucose levels.

While a trend toward improved eGFR was noted in the Mahmoud et al.[30] study, it did not reach statistical significance, except for the SGLT2i group, where an eGFR above 90 demonstrated significance ($p = 0.0135$). The typical decline in eGFR was observed in the SGLT2i group at 1-3 months. Additionally, there was a significant reduction in albuminuria in both study groups.

In this cohort, there was a slightly decreased throughout the follow-up in creatinine and uPCR values concerning renal graft function but not significantly ($p > 0.05$).

However, it is crucial to note that the use of GLP1RA is associated with potential adverse events, primarily gastrointestinal symptoms such as nausea, vomiting, and diarrhea so it requires careful consideration in KTR due to their impact on medication absorption. It is worth noting that GLP1RA delay gastric emptying, which may affect the absorption of immunosuppressant medications, because although GLP1RA do not engage in cytochrome or transporter-mediated drug-drug interactions, their effects on gastric emptying may influence tacrolimus absorption. Monitoring trough levels of tacrolimus is recommended when co-administered with GLP1RA.[1] There is a scarcity of data regarding the safety of GLP1RA in posttransplant individuals. A small case series involving five patients who received liraglutide alongside tacrolimus post-kidney transplant indicated no significant clinical impact on trough tacrolimus levels, which suggest a hypothesis that GLP1RA may be both safe and efficacious in the management of diabetes following transplantation.[1,4,27-29]

The occurrence of these symptoms is dose-dependent and varies based on the route of administration. Additionally, adverse events associated with GLP1RA, such as dehydration due to nausea and vomiting, can lead to decreased renal function. Other common adverse events include headache, nasopharyngitis, or injection site reactions were described, but these typically do not lead to treatment discontinuation.[1,4,27-29]

Despite these concerns, the study reports favorable results obtained with the administration of semaglutide to three transplant recipients with metabolic syndrome. Limited case series involving KTR have not reported any significant adverse effects or interactions with immunosuppressive drugs. However, the absence of RCTs investigating the safety and effectiveness of GLP1RA in this specific population remains a notable gap in the literature. Approaches to NODAT management rely heavily on extrapolating from the mechanisms, pharmacokinetics, and pharmacodynamics observed in native DM patients. This scarcity of data is particularly evident in novel diabetes medications like GLP1RA.[1,27-30]

Our study is limited by the wide range of follow-up time (4 to 101 months), potentially causing varied outcomes and difficulties in accurately assessing disease progression trends, introducing variability in CKD severity and duration and uPCR levels during assessment.

CONCLUSION

Diabetes mellitus affects a significant global population, and its prevalence is on the rise. The condition is closely associated with enduring vascular complications, and specifically, T2DM independently heightens the risk of adverse CV outcomes. Implementing effective strategies to mitigate complications is paramount in the overall management of diabetes.

This data illustrate that the utilization of GLP1RA is not only viable but also well-tolerated among KTR, which presents an opportunity for exploring innovative therapeutic approaches to enhance long-term outcomes following kidney transplantation. GLP1RA is a viable option for managing diabetes in KTR, with careful monitoring of drug interactions and potential side effects. Larger and more extended studies on GLP1RA are crucial for a comprehensive understanding of their efficacy over the long term.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Silvano J, Ribeiro C, Malheiro J, Pedroso S, Almeida M; **Conception and design:** Freitas JC, Martins LS; **Data analysis and interpretation:** Fonseca I, Malheiro J; **Article writing:** Freitas JC; **Critical revision:** Silvano J; **Final approval:** Martins LS.

DATA AVAILABILITY STATEMENT

All dataset were generated or analysed in the present article study.

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