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Safety and efficacy of semaglutide in post kidney transplant patients with type 2 diabetes or Post-Transplant diabetes

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ABSTRACT

Objective: Type 2 diabetes mellitus (T2DM) and post-transplant diabetes mellitus (PTDM) are common in renal transplant recipients. Semaglutide has demonstrated efficacy and safety in patients with T2DM. To date, only a limited number of studies have investigated its use in renal transplant patients. This study assessed the safety and efficacy of semaglutide in post-renal transplant patients.

Methods: A retrospective study was conducted at king Abdulaziz Medical City-Riyadh, Saudi Arabia. The subjects of the study were adults and adolescents (>14 years) who had undergone a kidney transplant and had pre-existing T2DM or PTDM. The study subjects were given semaglutide during the study period, from January 2018 to July 2022. The data were collected over a period of 18 months.

Results: A total of 39 patients were included, 29 (74 %) of whom were male. A significant decrease in hemoglobin A1c (HbA1c) was observed during the follow-up period when compared to baseline (8.4 %±1.3 % at baseline vs. 7.4 %±1.0 % at 13–18 months ($p < 0.001$). A significant reduction in weight was also noted at follow-up as compared to baseline (99.5 kg ± 17.7 vs 90.7 kg ± 16.8 at 13–18 months ($p < 0.001$). No significant changes were found in renal graft function markers.

Conclusion: Semaglutide was found to significantly reduce HbA1c levels and weight in post renal transplant patients with diabetes. No significant changes in markers of renal graft function were observed.

Introduction

Diabetes is becoming a growing international health crisis, and its frequency is increasing in both prevalence and associated complications [1]. Type 2 diabetes mellitus (T2DM) is common in the post-renal transplant setting as either pre-existing T2DM or new-onset post-transplant diabetes (PTDM). According to estimates, 20–38 % of patients undergoing kidney transplantation have T2DM. Up to 22.5 % of kidney transplant patients develop diabetes after the transplant [2]. Glycemic control in patients with diabetes post renal transplant is of paramount importance to maintain normal graft function [3].

The management and treatment protocols for T2DM are constantly evolving with new approaches and novel antidiabetic agents. Glucagon-likepeptide-1 (GLP-1) receptor agonists (GLP-1RAs) are effective in managing T2DM. These drugs mimic the incretin hormone GLP-1, which is released from the gut to stimulate insulin release and inhibit glucagon release [4]. Moreover, GLP-1RA induces satiety and decreases gastric motility. These agents thus effectively decrease blood glucose levels by reducing gastric emptying and food intake while increasing insulin release. As a result, hemoglobin A1c (HbA1c) levels decrease, and favorable outcomes in body weight, blood pressure, and lipid profile are seen [5,6].

One potent GLP-1 analog is semaglutide. It is a long-acting GLP-1RA that is administered either once a week subcutaneously, or orally daily [7]. When injected, it has a maximum bioavailability of 89 % after 56 h. Semaglutide is closely related to the homology of GLP-1, with a few alterations. These alterations lead to a half-life of 165 h. Furthermore, semaglutide is metabolized via proteolysis and β oxidation, and it is then

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partially eliminated through urine by the kidneys [8,9].

Semaglutide is generally considered a safe medication; however, it may cause mild to moderate gastrointestinal side effects, such as nausea, vomiting, and diarrhea. Due to its weight loss effect, semaglutide may also increase the risk of developing cholelithiasis [10]. Trials have shown a significant reduction in both HbA1c and body weight with semaglutide [11]. The nephroprotective role of semaglutide has also been documented [12,13].

The use of GLP-1RAs for T2DM or PTDM in patients who have had a renal transplant has generally not been well studied. Multiple small-scale studies have demonstrated the safety and efficacy of GLP-1RAs in this population, but only a few patients in these studies were on semaglutide [14,15]. This study thus aims to evaluate the safety and efficacy of semaglutide in post-kidney transplant patients who have pre-existing T2DM or PTDM.

Methods

This is a retrospective chart review cohort study conducted at king Abdulaziz Medical City-Riyadh, Saudi Arabia. The study participants were all adults and adolescents (>14 years) who were post-kidney transplant patients with T2DM or PTDM and on semaglutide between January 2018 and July 2022. PTDM was diagnosed based on the American Diabetes Association's diabetes-range hyperglycemia by testing random glucose or fasting glucose, HbA1C, and whether the patient was on oral hypoglycemic agents and/or insulin that was started after the kidney transplant. The study was conducted only after ethical approval was obtained by the Institutional Review Board (IRB) with the approval number of IRB/2424/22.

Data were collected from the patients' medical records and input into an Excel spreadsheet. SPSS V20 software was used for the data analysis. Demographic and clinical data such as age, gender, type of renal transplant, comorbid conditions, medications, weight, creatinine level, eGFR, HbA1c, and albumin-creatinine ratio (ACR) were collected at baseline and at intervals of 3–6 months for up to 18 months after semaglutide initiation.

Frequencies and percentages were used to describe the categorical variables. The mean and standard deviation were used to describe normally distributed numerical variables, while the median and interquartile ranges were used to describe the skewed data of numerical variables.

Paired *t*-test was used to compare the means of the numerical variables of the normally distributed data. Wilcoxon test was used to compare the medians of the skewed data. A P value of less than 0.05 was considered significant.

Results

A total of 39 participants met the inclusion criteria of being post-renal transplant patients and on semaglutide for diabetes. Twenty-nine patients (74 %) were male. The mean age was 54 ± 9 years.

About 21 (54 %) patients had pre-transplantation T2DM, with a median duration of 18 (IQR 11, 27) years before transplant. The remaining 18 patients (46 %) had PTDM, with a median duration of 9.5 (IQR 6, 12) years post-transplantation. The majority of the patients, 23 (59 %), underwent living related renal transplantation, while nine patients (23 %) and seven patients (18 %) underwent living non-related renal transplants and deceased donor renal transplants, respectively. A large number of the total study sample, 36 (92 %) people, had hypertension. A total of 16 patients (41 %) had diabetes retinopathy at baseline. The majority of the study sample, 33 patients (85 %), were on insulin. Eight patients (21 %) were on dipeptidyl peptidase-4 inhibitors (DPP-4i), which was discontinued upon semaglutide initiation (Table 1). Out of 39 patients, 37 (95 %) were on prednisone, mycophenolate mofetil, and tacrolimus, one patient was on prednisone, mycophenolate mofetil, and cyclosporine, and another patient was on mycophenolate mofetil and tacrolimus without prednisone. Patients with pre-transplant diabetes received semaglutide after a median of 37 (IQR 21, 58) months after their kidney transplants, while patients with PTDM received semaglutide after a median of 118 (IQR 64, 158) months after their kidney transplants. Two patients (5 %) received semaglutide as early as four months post kidney transplant.

Table 1
Baseline characteristics (at the time of semaglutide initiation).

		N (39)	%
Gender	Male	29	74 %
	Female	10	26 %
Diabetes in relation to renal transplant	Pre-transplant	21	54 %
	Post-transplant	18	46 %
Type of kidney transplant	Deceased donor renal transplant	7	18 %
	Living related renal transplant	23	59 %
	Living non-related renal transplant	9	23 %
Smoking		2	5 %
Hypertension		36	92 %
Dyslipidemia		31	79 %
Ischemic heart disease		8	21 %
Diabetes Retinopathy at baseline		16	41 %
Neuropathy		8	21 %
Diabetic foot ulcer		1	3 %
Anti-hyperglycemic agents			
Insulin		33	85 %
Metformin		19	49 %
SGLT2i		4	10 %
DPP4i*		8	21 %
Sulfonylurea		8	21 %

SGLT2: sodium glucose transporter 2 inhibitor.
DPP4i: dipeptidyl peptidase 4 inhibitor.
* All DPP4i discontinued upon semaglutide initiation

The mean HbA1c was 7.4 %±0.9 % at the 3–6 months' follow-up compared to 8.5 %±1.3 % at baseline (P value 0.003), n = 36. The mean HbA1c was 7.3 %±1.0 % at the 7–12 months' follow-up compared to 8.5 %±1.3 % at baseline (P value 0.019), n = 33. The mean HbA1c was 7.4 %±1.0 % at 13–18 months' follow-up compared to 8.4 %±1.3 % at baseline (P value < 0.001), n = 31 (Table 2).

For weight, the mean weight at follow-up after 3–6 months was 92.3 ± 14.7 kg (203.5 ± 32.4 lb) compared to 95.7 ± 15.6 kg (211.0 ± 36.6 lb) at baseline (P value < 0.001), n = 37. The mean weight at follow-up

Table 2
Hemoglobin A1C (%) at follow up compared to baseline.

	n	Mean	SD	P-value*
HBA1C at baseline	36	8.5	1.3	0.003
HBA1C at 3–6 months		7.4	0.9	
HBA1C at baseline	33	8.5	1.3	0.019
HBA1C at 7–12 months		7.3	1.0	
HBA1C at baseline	31	8.4	1.3	<0.001
HBA1C at 13–18 months		7.4	1.0	

*P-value calculated using paired T-test.

after 7–12 months was 91.1 ± 14.3 kg (200.8 ± 31.5 lb) compared with 96.9 ± 16.1 kg (213.6 ± 35.5 lb) at baseline (P value < 0.001), n = 34. The mean weight at 13–18 months' follow-up was 90.7 ± 16.8 kg (200.0 ± 37.0 lb) compared with 99.5 ± 17.7 kg (219.4 l ± 39.0 lb) at baseline (P value < 0.001), n = 23 (Table 3).

In terms of kidney function markers, the median eGFR was 75.5 ml/min/1.73 m^2 at 3–6 months' follow-up compared to 75.5 ml/min/1.73 m^2 at baseline (P value 0.724), n = 38. The median eGFR was 75.0 ml/min/1.73 m^2 at 7–12 months' follow-up compared to 72.0 ml/min/1.73 m^2 at baseline (P value 0.443), n = 33. The median eGFR was 77.0 ml/min/1.73 m^2 at 13–18 months' follow-up compared to 72.0 ml/min/1.73 m^2 at baseline (P value 0.976), n = 23 (Table 4). Similarly, there was no significant difference in creatinine upon follow-up compared to baseline. The median creatinine level was 93.0 mmol/l at 3–6 months' follow-up compared to 90.0 mmol/l at baseline (P value 0.432), n = 38. The median creatinine level was 89.0 mmol/l at 7–12 months' follow-up compared to 90.0 mmol/l at baseline (P value 0.741), n = 33. The median creatinine level was 90.0 mmol/l at 13–18 months' follow-up and at baseline (P value 0.648), n = 23, (Table 5). The albumin creatinine ratio (ACR) was available in a few patients at different follow-up points and baseline. The median ACR level was 2.70 mg/mmol at 3–6 months' follow-up compared to 6.15 mg/mmol at baseline (P value 0.182), n = 12. The median ACR level was 4.20 mg/mmol at 7–12 months' follow-up compared to 9.0 mg/mmol at baseline (P value 0.477), n = 11. The median ACR level was 5.60 mg/mmol at 13–18 months' follow-up compared to 6.85 mg/mmol at baseline (P value 0.093), n = 8, (Table 6). Out of 33 patients who were on insulin, 12 (36 %) were able to reduce their insulin doses after starting semaglutide. The median total daily insulin dose was 117.5 units before initiating semaglutide and was reduced to 66 units at the last follow-up. The median difference was 51.5 units (P = 0.007). Four patients (12 %) required an increase in insulin doses to control their blood glucose levels after starting semaglutide. Their insulin doses increased by 4, 22, 44, and 78 units, respectively. The remaining 17 patients (52 %) continued taking the same total daily insulin dose.

In terms of semaglutide tolerability, two patients (5 %) discontinued the medications due to side effects, specifically nausea and vomiting. Four patients (10 %) did not receive the full dose of semaglutide, two of them (5 %) had their dose kept at 0.5 mg based on the treating physician's decision, as they did not experience any side effects. The other two patients (5 %) experienced side effects, specifically nausea and diarrhea, when taking the full dose of 1 mg. However, their symptoms improved after the dose was reduced to 0.5 mg. The remaining 33 patients (80 %) were able to tolerate the full dose of 1 mg of semaglutide, and only two patients (6 %) among them reported side effects in the form of fatigue and diarrhea. However, both patients' symptoms improved over time, and they continued taking semaglutide at the full dose.

During the follow-up period, 37 patients (95 %) maintained the same dose of tacrolimus, with a median dose of 2 mg (IQR 1.5, 3.0). The mean tacrolimus level remained stable at 7.2 ng/ml ± 2.2 throughout the study. Two patients (5 %) started semaglutide four months after their transplant, and their tacrolimus doses were adjusted as expected. The first patient's tacrolimus dose was reduced from 15 mg prior to semaglutide initiation to 6 mg at the last follow-up, and the second patient's dose was reduced from 8 mg prior to semaglutide initiation to 4 mg during the follow-up. Two patients underwent a transplanted kidney biopsy, with one patient showing no evidence of rejection and the other showing chronic rejection.

Table 3
Weight at follow up compared to baseline.

	n	Mean	SD	P-value*
Weight at baseline, kg(lb)	37	95.7(211.0)	15.6(36.6)	<0.001
Weight at 3–6 months, kg(lb)		92.3(203.5)	14.7(32.4)	
Weight at baseline, kg(lb)	34	96.9(213.6)	16.1(35.5)	<0.001
Weight at 7–12 months, kg(lb)		91.1(200.8)	14.3(31.5)	
Weight at baseline, kg(lb)	23	99.5(219.4)	17.7(39.0)	<0.001
Weight at 13–18 months, kg(lb)		90.7(200.0)	16.8(37.0)	

*P-value calculated using paired T-test.

Table 4
eGFR(mL/min/1.73 m2) at follow up compared to baseline.

	n	Median	IQR	P-value*
eGFR at baseline	38	73.50	58.75–85.75	0.724
eGFR at 3–6 months		75.5	62.25–90.0	
eGFR at baseline	33	72.0	58.5–84.0	0.443
eGFR at 7–12 months		75.0	63.5–98.5	
eGFR at baseline	23	72.0	59.0–85.0	0.976
eGFR at 13–18 months		77.0	54.0–84.0	

*P-value calculated using Wilcoxon test.

Table 5
Creatinine(mmol/l) at follow up compared to baseline.

	n	Median	IQR	P-value*
Creatinine at baseline	38	90.0	73.75–111.75	0.432
Creatinine at 3–6 months		93.0	76.75–11.25	
Creatinine at baseline	33	90.0	74.0–116.0	0.741
Creatinine at 7–12 months		89.0	74.5–108.0	
Creatinine at baseline	23	90.0	74.0–118.0	0.648
Creatinine at 13–18 months		90.0	75.0–134.0	

*P-value calculated using Wilcoxon test.

Table 6
Albumin/creatinine ratio (ACR) (mg/mmol) at follow up compared to baseline.

	n	Median	IQR	P-value*
ACR baseline	12	6.15	2.95–18.05	0.182
ACR at 3–6 months		2.70	1.23–24.0	
ACR at baseline	11	9.0	4.20–20.90	0.477
ACR at 7–12 months		4.20	2.90–13.8	
ACR at baseline	8	6.85	3.55–54.5	0.093
ACR at 13–18 months		5.60	1.70–40.18	

*P-value calculated using Wilcoxon test.

Discussion

Diabetes is a common complication of renal transplantation. It occurs as a pre-existing condition before renal transplantation or as a post-transplant complication in the form of PTDM. PTDM is the latest terminology for what was previously known as new-onset diabetes after transplantation (NODAT). The NODAT diagnosis is based on the documentation of hyperglycemia in the diabetes range through OGTT, random glucose, fasting glucose, or HbA1c tests. However, HbA1c should not be used within the first 45 days of transplant, as it may not be accurate. In addition, the requirement for insulin or oral hypoglycemic agents during the post-transplant period defines NODAT. A more inclusive term is PTDM, as it encompasses all cases of hyperglycemia in post-transplant patients, even if not discovered before transplant [16–18].

In this study, 46 % of the patients had PTDM/NODAT, which means that they were diagnosed with diabetes after transplantation. This finding is consistent with other studies that reported that 30–50 % of patients with renal transplants develop PTDM [19–21]. The high PTDM prevalence is linked to classic T2DM risk factors, such as older age and obesity, which are common among renal transplant recipients. Moreover, post-transplant risk factors, such as immunosuppressive therapy, further increase the risk of PTDM development [14,21]. In this study, most patients (59 %) underwent living related renal transplantation, while 23 % and 18 % underwent living unrelated renal transplant and deceased donor renal transplant, respectively. There have been

contradictory findings regarding the association between the type of transplanted kidney and PTDM. Some studies have suggested that deceased kidney transplantation is associated with a higher risk of diabetes development [22]. On the contrary, other studies have reported no association between transplanted kidney type and PTDM development [23].

In general, PTDM shares many features with T2DM in terms of patients' clinical profiles and, to some extent, the pathophysiological mechanisms and management approaches [24–26]. Insulin is mainly used to manage diabetes in the renal transplant setting, whether for pre-existing T2DM or PTDM, as it is effective and safe when used in the early and late post-transplant phases [26]. However, the development of newer agents with particularly favorable renal outcomes has led to their use, in addition to insulin, in the management of T2DM and PTDM after renal transplantation [24–26].

Semaglutide has shown significant efficacy in the management of T2DM, as demonstrated in several clinical trials, such as the SUSTAIN clinical trials program. A significant reduction in HbA1c levels and a significant reduction in body weight was observed with semaglutide compared to placebo and other treatment arms [10,11]. GLP-1RAs in general and semaglutide in particular are prescribed more frequently for kidney transplant patients with diabetes [13,25].

In this study, semaglutide use in renal transplant patients, in addition to other anti-hyperglycemic agents, significantly decreased HbA1c levels and weight in the first 3–6 months. This effect was maintained for up to 18 months after semaglutide initiation. A significant decrease in HbA1c was observed by an average of approximately 1 % from baseline at all follow-up periods. Weight also decreased significantly by 3.5–6 kg (7.7–13.2 lb) during the first year of follow-up and by up to 8.8 kg (19.4 lb) after 12–18 months of follow-up. One-third of patients were able to reduce their total insulin dosage, with a median reduction of 51.5 units (43 %), while four patients required higher insulin doses for glycemic control after semaglutide initiation. The use of semaglutide did not significantly change the renal graft function markers across the multiple follow-up periods. While there were numerically lower ACR values at the follow ups, this difference was not statistically significant. Additionally, all the patients continued taking the same immunosuppressive therapy with stable tacrolimus levels. These results are consistent with the conclusions of other studies that say that GLP-1RAs are safe and effective in controlling blood glucose and reducing weight in renal transplant recipients [14,24,27,28].

A study conducted by Kukla et al. examined the effect of liraglutide, exenatide, or dulaglutide on 14 patients who had diabetes and undergone a renal transplant. They reported a non-significant median weight loss of 0.95 kg and a non-significant median reduction of HbA1c by 0.4 %. However, the study showed that the insulin dose had to be significantly reduced by 30 units [14]. The dose and level of tacrolimus did not significantly change, and all the patients had stable renal functions with stable eGFR and proteinuria at 12 months after starting GLP-1RA. Another study by González et al. included 15 patients post-kidney transplant who were treated using GLP-1RA. Seven patients were on semaglutide. The study reported a non-significant median HbA1c reduction of 0.7 % but a significant mean weight loss of 7.2 kg. In the seven patients, there was a reduction in insulin and antidiabetic medications but no change in immunosuppressive therapy or kidney functions [28].

Sweiss et al., on the other hand, reported significant HbA1c and weight reduction in patients who were treated with GLP-1RAs, mainly liraglutide, after a kidney, liver, or lung transplant with no significant alteration in immunosuppressive therapy [15]. Notably, previous studies included patients on different GLP-1RAs with only a few patients (2–7) on semaglutide.

Semaglutide is generally a well-tolerated medication, with gastrointestinal side effects being the most commonly reported adverse effect. In this study, only a few patients experienced gastrointestinal side effects. However, only two patients discontinued the medication, and two other patients were unable to continue taking the full dose. This is consistent with other studies that reported generally good tolerability of semaglutide and other GLP-1RAs in renal and solid organ transplant recipients [14,24]. According to Kukla et al., out of 17 patients who were taking GLP-1RAs (mainly liraglutide), five patients stopped the medication due to gastrointestinal side effects and malaise, while two other patients stopped due to pancreatitis and its inefficacy in controlling diabetes [14]. Similarly, Swiss et al. reported a low rate of side effects, with only 7 % of patients reporting nausea [15]. In the present study, semaglutide was not titrated to the full dose, although there were no side effects. This alludes to common physician inertia phenomena encountered in diabetes care [29].

These findings collectively suggest that semaglutide is effective in reducing HbA1c and weight in post-transplant patients with T2DM or PTDM. In addition, semaglutide possibly has a stabilizing effect on kidney function. Notably, in the SUSTAIN-6 trial, semaglutide resulted in a significant reduction in the incidence of new or worsening of existing nephropathy [30]. Similarly, a post-hoc analysis of the SUSTAIN-6 and POINEER-6 trials of semaglutide suggested that it has a stabilizing effect on kidney function [31]. Therefore, it is possible that, just like in patients with native kidneys, semaglutide could benefit renal grafts in renal transplant patients and be worth investigating further.

Our study is important as it examined the use of semaglutide, a highly effective medication, in renal transplant patients who are at a high risk for diabetes complications. The study included a relatively large sample size, with all the patients receiving semaglutide, and a longer follow-up duration compared to previous studies. However, the study has limitations as it was retrospective and conducted in a single center. Hence, further prospective studies with a control arm and more, extended follow-up durations are necessary to assess the benefits of semaglutide in renal transplant patients.

Conclusion

Our study has revealed that semaglutide is effective and provides significant and sustained reductions in HbA1c levels in post-renal transplant patients with T2DM or PTDM. Similarly, semaglutide led to a sustained reduction in weight. Renal graft function markers were stable during the study period. Semaglutide was well tolerated and led to no significant side effects.

Clinical Relevance

This study highlights the safety and efficacy of semaglutide use in post-renal transplant patients. Semaglutide has been found to be effective in post kidney transplant patients with type 2 diabetes or post-transplant diabetes. semaglutide provides significant and sustained reductions in both HbA1c levels and weight. No negative impact of semaglutide was observed on renal graft function markers.

Author statement

Moeber Mahzari, Omar Alluhayyan, Yazeed Alrayani, Mahdi Almutairi and Mohammed Bayounis designed the study. Moeber Mahzari, Omar Alluhayyan, Yazeed Alrayani, Mahdi Almutairi and Mohammed Bayounis worked on the methodology. Omar Alluhayyan, Yazeed Alrayani, Mahdi Almutairi and Mohammed Bayounis worked on the data curation. Moeber Mahzari and Amir Omair did the statistical analysis. Moeber Mahzari, Omar Alluhayyan, Yazeed Alrayani, Mahdi Almutairi and Mohammed Bayounis wrote the first draft. Moeber Mahzari and Awad Alshahrani revised the manuscript. Moeber Mahzari and Awad Alshahrani did the study supervision. All authors contributed and approved the final version of the paper.

CRediT authorship contribution statement

Moeber Mohammed Mahzari: . Omar Buraykan Alluhayyan: . Mahdi Hamad Almutairi: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Mohammed Abdullah Bayounis: . Yazeed Hasan Alrayani:** Writing – original draft, Methodology, Data curation, Conceptualization. **Amir A. Omair:** Visualization, Validation, Software, Methodology, Formal analysis. **Awad Saad Alshahrani:** Writing – review & editing, Supervision, Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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