Original Article

The impact of weekly semaglutide, a glucagon-like peptide-1 agonist, on kidney outcomes in adults with type 2 diabetes mellitus

Ahmad A. Algarni[1], Fahad S. Alqarni[2], Hanin A. Shalaby[3]

[1]Consultant Family Medicine, King Fahad Armed Forces Hospital, Jeddah, Kingdom of Saudi Arabia, [2]Department of Family Medicine, King Fahad Armed Forces Hospital, Jeddah, Kingdom of Saudi Arabia, [3]Clinical Research and Data Management, King Fahad Armed Forces Hospital, Jeddah, Kingdom of Saudi Arabia

Abstract

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder associated with kidney complications. This study aims to investigate the effects of weekly subcutaneous semaglutide, a GLP-1 agonist, on kidney outcomes. **Methods:** This retrospective cohort study was conducted in nephrology and endocrinology clinics at KFAFH from March 2022 to February 2023. The sample size was determined based on hospital records, and randomly selected patients who met the inclusion criteria were included. The inclusion criteria included adults with T2DM who were on weekly subcutaneous semaglutide for 6 months or longer. Patients with type 1 diabetes mellitus, pregnant or gestational diabetes patients, individuals who added other antidiabetic medications during the study period, and participants who refused to be involved were excluded from the study. **Results:** The study included participants aged between 42 and 85 years, with a mean age of 65.38 years, and the majority (58.7%) were males. There was a significant weight and BMI reduction observed in all patients, with *P* values <0.001 for both. The average weight reduction was 2.97 kg (SD = 2.34, 95% CI 1.65–3.30), and the average Body (BMI) reduction was 1.16 (SD = 0.91, 95% CI 1.03–1.29). A vast majority of participants (98.5%) reported a weight loss of at least 1 kg, and 13.8% of participants experienced a change in BMI category from higher to lower. No patients reported an increase in the BMI category. There was a significant reduction in glycohemoglobin (HbA1c) measurements from 9.18 pretreatment to 8.13 posttreatment, with an average reduction of 1.05 units (SD = 1.84, 95% CI 0.79–1.31). The majority of participants (70.9%) reported a reduction in HbA1c of at least 0.1 unit. Although there was a slight decrease in estimated glomerular filtration rate (eGFR) values on average (1.35 units), the change was not statistically significant (*P* = 0.059). More than half of the participants (51.5%) reported an increase in eGFR, 45.4% reported a decrease, and 3.1% reported no change. There was a statistically significant reduction in urinary albumin-to-creatinine ratio (UACR) values from a median of 5.97 pretreatment to a median of 5.60 post-treatment. The median decrease was 0.72 units, with one-third (33.3%) reporting an increase and two-thirds (66.7%) reporting a decrease in values. The correlation analysis revealed no significant association between the total quantity of semaglutide taken and the magnitude of changes. **Conclusion:** Our study on the impact of weekly semaglutide in adults with T2DM reveals positive effects on kidney outcomes, including weight loss, glycemic control and improved urine albumin creatine ratio, and a reduced risk of nephropathy. These findings highlight the potential of semaglutide as a safe and effective treatment option for improving renal health in individuals with T2DM.

Keywords: Albuminuria, chronic kidney disease, eGFR, glucagon-like peptide-1 receptor agonists, semaglutide, type 2 diabetes

Address for correspondence: Dr. Fahad S. Alqarni, Department of Family Medicine Department, King Fahad Armed Forces Hospital, 6340 – Al Kawthar Dist., Jeddah, Kingdom of Saudi Arabia.
E-mail: dr.fahadsalem@hotmail.com

Received: 22-06-2023 **Revised:** 19-07-2023
Accepted: 11-08-2023 **Published:** 06-03-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1031_23

Introduction

Chronic kidney disease (CKD) is a common complication in patients with type 2 diabetes (T2D), affecting approximately 23–43% of individuals.[1] Currently, diabetes is the leading

How to cite this article: Algarni AA, Alqarni FS, Shalaby HA. The impact of weekly semaglutide, a glucagon-like peptide-1 agonist, on kidney outcomes in adults with type 2 diabetes mellitus. J Family Med Prim Care 2024;13:532-6.

cause of end-stage kidney disease (ESKD) that necessitates renal replacement therapy.[1] With the rising global prevalence of T2D, there is a corresponding increase in the occurrence of kidney failure. It is projected that by the year 2030, the number of individuals affected by kidney failure will surpass 5 million worldwide.[2] Additionally, albuminuria, an early indicator of kidney damage, is present in 17–26% of patients at the time of T2D diagnosis.[3] Notably, individuals with T2D and CKD who develop macroalbuminuria face a higher risk of cardiovascular disease mortality compared to the progression of ESKD.[4]

Various research groups, including the Steno group, have demonstrated that a comprehensive approach to managing T2D with microalbuminuria can effectively slow down the progression of nephropathy and reduce the loss of renal function. This approach involves implementing a healthy lifestyle, early control of metabolic hyperglycemia, blood pressure, and weight.[5] Moreover, in recent years, studies have revealed the beneficial effects of specific drug classes such as renin–angiotensin–aldosterone system inhibitors, glucagon-like peptide-1 receptor agonist (GLP-1 RAs), and sodium-glucose cotransporter-2 inhibitors in delaying or minimizing both microvascular and macrovascular damage associated with CKD in T2D patients.[6,7]

Recent advancements in the treatment of T2D have revealed therapeutic options that effectively decrease the progression of diabetic kidney disease (DKD). Clinical trials focusing on cardiovascular outcomes have demonstrated that sodium-glucose cotransporter-2 inhibitors and GLP-1 RAs significantly reduce the risk of major adverse cardiovascular events.[8,9] Moreover, these trials have also indicated potential kidney-related benefits as secondary outcomes.[10] The initial T2D kidney outcome trials specifically targeted the use of sodium-glucose cotransporter-2 inhibitors, canagliflozin, and dapagliflozin, and demonstrated a considerable reduction in the risk of adverse kidney outcomes when compared to the administration of a placebo. Notably, both trials included patients with and without T2D.[11]

This study was designed to determine the kidney outcomes in adults with type 2 diabetes mellitus (T2DM) receiving weekly subcutaneous semaglutide for 12 months in real-world clinical settings and determine response variations between preexisting kidney dysfunction and normal function.

Material and Methods

This retrospective cohort study aimed to assess the kidney outcomes of adults aged 18 and above with T2DM who received weekly subcutaneous semaglutide for at least 6 months. The study population consisted of patients attending the primary care, nephrology, and endocrinology clinics at KFAFH. The inclusion criteria included adults with T2DM who were on weekly subcutaneous semaglutide for 6 months or longer. Patients with type 1 diabetes mellitus, pregnant or gestational diabetes patients, individuals who added other antidiabetic medications during the study period, and participants who refused to be involved were excluded from the study.

The sample size was determined using the hospital recording system, and patients who met the inclusion and exclusion criteria and provided consent were randomly selected and included in the study.

The study obtained ethical approval from the Hospital Research Ethical Committee at King Fahd Armed Forces Hospital in Jeddah. Patient medical records were reviewed within the period from March 2022 to February 2023, ensuring confidentiality. Demographic data (age, gender, height, weight, and body mass index) and clinical data (estimated glomerular filtration rate (eGFR), urine albumin, creatinine ratio, glycohemoglobin (HbA1c)) before and at 6 and 12 months after semaglutide treatment were investigated. Information on insulin intake was also collected.

The collected data were tabulated and analyzed using descriptive statistics, including frequencies, percentages, means, and standard deviations. Paired-sample *t*-tests (and nonparametric equivalent—Wilcoxon's signed rank test) were used to compare numerical measurements between pre- and posttreatment. Categorical (ordinal) variables were compared using the sign test to evaluate change in categories from pre- to postassessments.

Statistical Package for Social Sciences version 20 (SPSS Inc., Chicago, IL, USA) was used for the analysis. A significance level of $P < 0.05$ was considered.

Results

Table 1 summarizes the participants' sociodemographic characteristics. It shows that the study participants are between 42 and 85 years of age (mean age = 65.38 years), majority (58.7%) males, and have an average height of 162.7 cm (ranging between 138 and 183 cm).

Table 2 reports the diabetic medication used by the participants which includes semaglutide and insulin therapy. It shows that all subjects received various doses of semaglutide (0.25–1 mg, mean = 0.75 mg) during different number of days (ranging between 1 and 25, average 18.33). Total quantity of semaglutide received ranged between 0.25 and 25 mg with the mean of 14.59 (SD = 8.31). Additionally, a vast majority ($n = 181$, 92.3%) of patients are on insulin therapy.

Table 3 demonstrates the changes in the medical characteristics and clinical data. It displays significant weight and BMI reduction was observed for all patients, $P < 0.001$ and $P < 0.001$, respectively. Average weight reduction is 2.97 kg (SD = 2.34, 95% CI 1.65–3.30). Average BMI reduction is 1.16 (SD = 0.91, 95% CI 1.03–1.29). The vast majority of participants (98.5%) reported weight loss of at least 1 kg. About 13.8% of participants reported a change in BMI category from higher to lower one. No patients reported an increase in BMI category.

HbA1c measurements reduced significantly from 9.18 pretreatment to 8.13 post-treatment, with the average reduction of 1.05 units (SD = 1.84, 95% CI 0.79–1.31). Majority of participants (70.9%) reported reduction in HbA1c of at least 0.1 unit.

eGFR values decreased slightly (1.35 units on average); however, the change was not statistically significant, $P = 0.059$. More than half (51.5%) of participants reported an increase in eGFR, 45.4% reported a decrease, and 3.1% no change. Considering the eGFR stage, majority of participants (60.7%) reported no change in their eGFR stage. Only 15.3% reported improvement in stage, while the remaining 24% reported disease progression. Change in the eGFR stage is not statistically significant, $P = 0.068$.

Urinary albumin-to-creatinine ratio (UACR) values do not follow a normal distribution; therefore, nonparametric analysis was performed (Wilcoxon's signed rank test is a nonparametric equivalent of paired-sample *t*-test). We found a statistically significant reduction in UACR values from median 5.97 pretreatment to median 5.60 posttreatment. Median decrease was 0.72 units, with one-third (33.3%) reported increase and two-thirds (66.7%) decrease in values. Considering ACR stage, majority of participants (76.2%) reported no change in their ACR stage. Only 5.7% reported increase in stage (A1 → A2, A2 → A3), while the remaining 18.1% reported disease in stage (A2 → A1, A3 → A2). The overall change in the ACR stage is statistically significant, $P = 0.015$.

Correlation analysis was performed to examine the association between the total quantity of semaglutide taken and the magnitude of weight loss, BMI reduction, and decrease in HbA1c, eGFR UACR.

Table 4 addresses the association between semaglutide total quantity and changes in the clinical data. Correlation analysis shows no significant association between total quantity of semaglutide taken and magnitude of changes. All correlation coefficients are nonsignificant ($P > 0.05$). This suggests no dose–response effect of semaglutide.

Table 1: Demographic characteristics of study participants, *n*=196

	Mean±SD [range] or frequency (%)
Age (years)	65.38±8.82 [42–85]
Sex	
Female	81 (41.3%)
Male	115 (58.7%)
Height (cm)	162.70±9.16 [138–183]

Table 2: Semaglutide characteristics, *n*=196

	Mean±SD [range] or frequency (%)
Semaglutide dose (mg)	0.75±0.27 [0.25–1.00]
Semaglutide days taken	18.33±7.38 [1–25]
Semaglutide total quantity (mg)	14.59±8.31 [0.25–25.00]
On insulin	181 (92.3%)

Discussion

Our study reveals that semaglutide not only facilitates weight loss and enhances glycemic control but also exhibits a favorable impact on the urine albumin creatine ratio. In a post-hoc analysis of data from the SUSTAIN 1–7 trials involving 8416 patients, Mann *et al.*[12] examined the impact of subcutaneous semaglutide on estimated glomerular filtration rate (eGFR), urine albumin creatine ratio (UACR), and renal adverse events. While semaglutide initially led to a decline in eGFR within the first 12–16 weeks of treatment, it stabilized thereafter, and the overall difference compared to other antidiabetic drugs and placebo over the entire observation period was not statistically significant. Additionally, the group of patients treated with semaglutide showed a decreasing trend in UACR values. Compared to placebo, the semaglutide arm demonstrated superior performance in terms of major adverse cardiovascular events (6.6% vs. 8.9%), glycemic control (mean HbA1c reduction of − 1.1% vs. −1.4%), weight loss (−3.6 kg vs. −4.9 kg), and the onset or progression of nephropathy (3.8% vs. 6.1%). Similar to the findings of the LEADER trial, the reduction in macroalbuminuria (up to 46%)

Table 3: Change in medical characteristics

	Mean±SD, median [IQR], or frequency (%)		Statistical test for change
	Pretreatment	Posttreatment	
Weight (kg)	86.69±19.33	83.72±19.24	*P*<0.001
BMI (kg/m²)	33.07±6.23	31.91±6.26	*P*<0.001
BMI category			*P*<0.001
Normal	14 (7.1%)	27 (13.8%)	
Overweight	50 (25.6%)	52 (26.5%)	
Obesity	132 (67.3%)	117 (59.7%)	
HbA1c	9.18±1.79	8.13±1.71	*P*<0.001
eGFR[1]	48.07±13.36	46.72±11.44	*P*=0.059
CKD stage			
Stage 2	26 (13.3%)	8 (4.1%)	*P*=0.068
Stage 3a	96 (49.0%)	114 (58.2%)	
Stage 3b	59 (30.1%)	59 (30.1%)	
Stage 4	14 (7.1%)	12 (6.1%)	
Stage 5	1 (0.5%)	3 (1.5%)	
UACR[2]	5.97 [32.68]	5.60 [26.23]	*P*=0.005
UACR stage			
A1	33 (31.4%)	37 (35.2%)	*P*=0.015
A2	39 (37.2%)	44 (41.9%)	
A3	33 (31.4%)	24 (22.9%)	

Note: [1]eGFR values in "more than 60" category was assumed 75 (midpoint of 60–89 range); [2]UACR=urine albumin creatine ratio; [3]WSRT=Wilcoxon's signed rank test

Table 4: Association between semaglutide total quantity and changes in measurements

Outcome	Mean±SD, median [IQR]	Correlation with semaglutide total quantity (mg)
Weight loss (kg)	2.94±2.34	*P*=0.385
BMI reduction (kg/m²)	1.16±0.91	*P*=0.379
HbA1c decrease	1.05±1.84	*P*=0.109
eGFR decrease	1.35±9.92	*P*=0.618
UACR reduction	0.72 [4.48]	*P*=0.943

Note: r_s=Spearman's correlation coefficient

appears to be the primary mechanism through which semaglutide positively influences renal outcomes.[13]

The specific mechanisms underlying the potential kidney-protective effects of semaglutide remain uncertain. There are several potential mechanisms that could contribute to this effect, including natriuresis, reduction of oxidative stress, decreased inflammation and fibrosis, as well as hemodynamic effects.[14,15]

In a real-world study by Aviles Bueno *et al.*,[16] the effectiveness of subcutaneous semaglutide was examined in patients with T2DM and CKD. Over a 12-month period, the study found that semaglutide significantly improved glycemic control, resulted in weight loss, and reduced albuminuria, particularly in patients with macroalbuminuria. Furthermore, the administration of subcutaneous semaglutide was deemed safe and well tolerated in patients with DKD.[17]

In a multicenter study by Marbury *et al.*,[18] the pharmacokinetics and tolerability of subcutaneous semaglutide were assessed in subjects with varying degrees of renal function. The study found that semaglutide exposure was similar in subjects with mild/moderate renal impairment and end-stage renal disease, compared to those with normal renal function. Hemodialysis did not significantly affect the pharmacokinetics or tolerability of semaglutide.

GLP-1 receptor agonists, particularly long-acting agents like semaglutide, demonstrate high efficacy in lowering glucose levels by reducing fasting glucose and HbA1c levels.[19] They can reduce fasting glucose and HbA1c levels by approximately 0.5–1.5%. The efficacy depends on factors such as dosage, baseline HbA1c levels, background therapy, and the specific agent chosen.[20] Our study yielded comparable findings to these results.

One potential limitation of this study is its retrospective design, which relies on existing medical records and may be subject to incomplete or missing data. Additionally, the study's sample size and inclusion criteria may restrict the generalizability of the findings to a broader population of adults with T2DM.

Conclusion

Semaglutide demonstrated positive effects on renal parameters, including weight loss, good glycemic control and improvements in urine albumin creatine ratio, and a reduction in the onset or progression of nephropathy. Furthermore, semaglutide exhibited favorable safety and tolerability profiles in patients with DKD. These findings support the potential renal benefits of semaglutide as a treatment option for individuals with T2DM, emphasizing its potential to improve kidney outcomes in this patient population.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Martinez Martinez-Castelao A, Soler MJ, Navarro-González JF, Górriz JL. Will the new molecules be effective in renal and cardiovascular protection in diabetes mellitus and diabetic kidney disease? Nefrologia (Engl Ed) 2019;39:3-10.
2. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, *et al.* Worldwide access to treatment for end-stage kidney disease: A systematic review. Lancet 2015;385:1975-82.
3. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: Challenges, progress, and possibilities. Clin J Am Soc Nephrol 2017;12:2032-45.
4. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, *et al.* Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013;24:302-8.
5. Oellgaard J, Gæde P, Rossing P, Persson F, Parving HH, Pedersen O. Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits. Kidney Int 2017;91:982-8.
6. Magee C, Grieve DJ, Watson CJ, Brazil DP. Diabetic nephropathy: A tangled web to unweave. Cardiovasc Drugs Ther 2017;31:579-92.
7. Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, *et al.* Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: A meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:431-7.
8. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, *et al.* Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.
9. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
10. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, *et al.* SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9.
11. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, *et al.* Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46.
12. Mann JFE, Fonseca VA, Poulter NR, Raz I, Idorn T, Rasmussen S, *et al.* Safety of Liraglutide in type 2 diabetes and chronic kidney disease. Clin J Am Soc Nephrol 2020;15:465-73.
13. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, *et al.* Liraglutide and cardiovascular outcomes in type 2 diabetes 2016;375:311-22.
14. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, *et al.* Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. Circulation 2019;139:2022-31.
15. Muskiet MHA, Tonneijck L, Smits MM, van Baar MJB, Kramer MHH, Hoorn EJ, *et al.* GLP-1 and the kidney: From physiology to pharmacology and outcomes in diabetes. Nat Rev Nephrol 2017;13:605-28.

16. Aviles Bueno B, Soler MJ, Perez-Belmonte L, Jimenez Millan A, Rivas Ruiz F, Garcia de Lucas MD. Semaglutide in type 2 diabetes with chronic kidney disease at high risk progression-real-world clinical practice. Clin Kidney J 2022;15:1593-600.
17. Mann JF, Hansen T, Idorn T, Leiter LA, Marso SP, Rossing P, *et al.* Effects of once-weekly subcutaneous semaglutide on kidney function and safety in patients with type 2 diabetes: A post-hoc analysis of the SUSTAIN 1–7 randomised controlled trials 2020;8:880-93.
18. Marbury TC, Flint A, Jacobsen JB, Derving Karsbøl J, Lasseter K. Pharmacokinetics and tolerability of a single dose of semaglutide, a human glucagon-like peptide-1 analog, in subjects with and without renal impairment. Clin Pharmacokinet 2017;56:1381-90.
19. Norhammar A, Mellbin L, Cosentino F. Diabetes: Prevalence, prognosis and management of a potent cardiovascular risk factor. Eur J Prev Cardiol 2017;24 (3_Suppl):52-60.
20. Sorli C, Harashima SI, Tsoukas GM, Unger J, Karsbøl JD, Hansen T, *et al.* Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): A double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol 2017;5:251-60.