Efficacy and Safety of Semaglutide, a Glucagon-Like Peptide-1 Receptor Agonist in Real-Life: A Case Series of Patients in Maintenance Incremental Hemodialysis

José C. De la Flor a  Javier Deira Lorenzo b  Alexander Marschall c  Francisco Valga d  Tania Monzón Vázquez d  Elisa Ruiz Cícero a

a Department of Nephrology, Hospital Central Defense Gomez Ulla, Madrid, Spain; b Department of Nephrology, San Pedro de Alcantara Hospital, Caceres, Madrid, Spain; c Department of Cardiology, Central Defense Gomez Ulla Hospital, Madrid, Spain; d Department of Nephrology, Dr. Negrin University Hospital of Gran Canaria, Las Palmas de Gran Canaria, Spain

Keywords
Glucagon-like peptide-1 receptor agonists · Diabetic kidney disease · Incremental hemodialysis · Albuminuria · Residual kidney function

Abstract
The glucagon-like peptide-1 receptor agonists (GLP-1RA) are among the newest treatment options available for managing type 2 diabetes mellitus and slowing the progression of diabetes kidney disease (DKD). Subcutaneous (SC) semaglutide (Ozempic®) is a GLP-1RA with an extended half-life of approximately 1 week. GLP-1RA are highly effective in improving glycemic control and also show other beneficial effects such as increased natriuresis; decreased blood pressure and albuminuria; reduction of oxidative stress and inflammation; delay of gastric emptying and suppress appetite; the latter may result in significant weight loss. GLP-1RA can be used in patients with advanced-stage CKD; the European Medicines Agency has approved the use of all commercially available human GLP-1 analogs up to a minimal eGFR of 15 mL/min/1.73 m². However, studies of safety and use of these agents in renal replacement therapy are scarce. Therefore, herein we present 3 cases of patients with advanced DKD in maintenance incremental hemodialysis with 1 session per week to describe the efficacy and safety of the SC semaglutide treatment and the favorable effects on glycemic control, lowering HbA1c, albuminuria, weight, blood pressure control, and preservation of residual kidney function (RKF) during a 6-month follow-up in a hospital hemodialysis unit in Spain. These effects
could produce an improvement in morbidity and mortality and could also prevent albuminuria and preserve the RKF. This may allow our patients to maintain a weekly hemodialysis session and could facilitate their inclusion in the kidney transplant waiting lists.

**Introduction**

Diabetic kidney disease (DKD) is the leading cause of end stage renal disease (ESRD) worldwide [1]. The uncontrolled hyperglycemia of type 2 diabetes mellitus (T2DM) is directly related to the increased risk of both microvascular and macrovascular complications (ischemic heart disease, heart failure, stroke, and peripheral arterial disease). Furthermore, in subjects with youth-onset T2DM, the natural history of DKD is aggressive [2]; and exhibits gender-related variability with early obesity-related cardiometabolic risk [3]. Women present a greater prevalence of DKD risk factors [3]. Gembillo et al. [4] conducted a systemic review of the literature to establish gender differences in renal outcomes in users of the new hypoglycemic agents. Their systematic review demonstrated that the gap among sexes in DKD can be partially filled using new hypoglycemic drugs. It emphasizes that the analysis of sexual dimorphism could represent a cornerstone for the development of appropriate gender-specific therapies.

In addition, patients with DKD that develop macroalbuminuria are at greater risk of cardiovascular disease mortality than progression to ESRD [5]. Rates of diabetes-related complications have decreased significantly in recent decades. However, this trend cannot be observed with CKD that requires renal replacement therapy attributed to DKD [6]. This underscores the need for new treatments in order to improve the glycemic control, regardless of glomerular filtration rate (GFR), with low risk of hypoglycemia and the capability to reduce cardiovascular and renal risk in this population.

Given the reduced kidney function in the setting of DKD, antidiabetic treatment options are limited, especially in patients with maintenance hemodialysis. Furthermore, patients with DKD and ESRD are at increased risk of hypoglycemia due to reduced gluconeogenesis in the kidney and altered pharmacokinetics of oral and injectable hypoglycemic agents. The half-life of insulin is prolonged in these patients due to reduced renal clearance of insulin, further increasing the risk of hypoglycemia. Thus, in patients using insulin and/or oral anti-hyperglycemic agents, dynamic adjustments with drug dose reduction or drug switching are often necessary.

The GLP-1RA are among the newest treatment options available for managing of T2DM and slowing the progression of DKD [7]. Subcutaneous (SC) semaglutide (Ozempic®), a GLP-1RA with a 94% sequence homology to native human GLP-1, has an extended half-life of approximately 1 week [8]. In phase III trials in patients with T2DM, semaglutide has been shown to stimulate glucose-dependent insulin release and decrease glucagon secretion, thus contributing to an improvement of glycemic control and reduction of glycated hemoglobin (HbA1c) [9]. They also show other beneficial effects: increased natriuresis; decreased blood pressure and albuminuria; reduction of oxidative stress and inflammation; delay of gastric emptying and suppress appetite; the latter may result in significant weight loss [10–13]. However, studies of safety and use of these agents in hemodialysis are scarce. Therefore, herein we present 3 cases of patients with advanced DKD in maintenance incremental hemodialysis (iHD) with 1 session per week to describe the efficacy and safety of the SC semaglutide treatment during a 6-month follow-up in a hospital hemodialysis unit in Spain.
Case Series

Case 1

A 56-year-old man with DKD and ESRD initiated iHD with one session/week (240 min) due to uremic symptoms, poor blood pressure control, and moderate-to-severe hyperkalemia. Baseline characteristics are shown in Table 1. The patient had a body mass index (BMI) of 36.5 kg/m², HbA1c level of 8.5%, and was being treated with insulin detemir (32 IU), repaglinide (3 mg/day), and linagliptin (5 mg/day). We discontinued repaglinide and linagliptin and started semaglutide 0.25 mg once weekly. The doses were progressively increased to 1 mg in the

### Table 1. Baseline characteristics

| Demographics | All patients (n = 3) | P1 | P2 | P3 |
|--------------|---------------------|----|----|----|
| Age, (IQR), years | 66 (62.5–75.7) | 56 | 79 | 61 |
| Sex - male, n (%) | 50 | M | M | F |
| BMI, (IQR) Kg/m² | 37 (36.2–40.7) | 36.53 | 36.33 | 33.9 |
| Diabetes mellitus, n (%) | 100 | Yes | Yes | Yes |
| History of diabetes, years | 16.5 (12.7–19.5) | 18 | 20 | 12 |
| HbA1c level | 8.5 | 6.5 | 7.1 |
| Diabetic treatment | | | | |
| Insulin (%) | 75 | Yes | No | Yes |
| DPP4i (%) | 100 | Yes | Yes | Yes |
| Repaglinide (%) | 100 | Yes | Yes | Yes |
| Hypertension, n (%) | 100 | Yes | Yes | Yes |
| Comorbidity | | | | |
| Chronic obstructive pulmonary disease (%) | 75 | Yes | Yes | No |
| Obstructive sleep apnea syndrome (%) | 100 | Yes | Yes | Yes |
| Ischemic heart disease (%) | 25 | No | No | No |
| Retinopathy (%) | 100 | Yes | Yes | Yes |
| Dyslipidemia (%) | 100 | Yes | Yes | Yes |
| Antihypertensive treatment; n (%) | 100 | Yes | Yes | Yes |
| Dialysis details | | | | |
| Vascular access, n (%) | | | | |
| Tunneled CVCs | 75 | No | Yes | Yes |
| AVF native | 25 | Yes | No | No |
| Technical dialysis, iHD (%) | 75 | iHD | iHD | iHD |
| ESA (UI/week) | 9,000 (4,250–13,750) | 3,000 | 8,000 | 10,000 |
| Dialysis time (h/week) | NA | 4 | 4 | 4 |
| Dry weight, kg | 89 (91.2–111.7) | 98 | 105 | 81.5 |
| Ultrafiltration volume, mL | 900 | 800 | 300 | 1,000 |
| Blood flow rate, mL/min | 350 | 350 | 350 | 370 |
| Dialysis vintage (month) | 10 (0.5–48.7) | 2 | 0 | 18 |

AVF, arterio-venous fistula; BMI, body mass index; CVC, central venous catheter; DPP4i, dipeptidyl peptidase 4 inhibitor; ESA, erythropoiesis-stimulating agents; HbA1c, hemoglobin A1C; iHD, incremental hemodialysis; h, hours; P, patient; M, male; F, female.
12 weeks, with good tolerance and no episodes of hypoglycemia. Furthermore, the dose of insulin was gradually reduced to 10 IU of detemir. At 24 weeks, the patient presented a decrease in HbA1c, weight, and BMI of 23.5%, 10.2%, and 10.5%, respectively (shown in Fig. 1a, b).

Case 2
A 79-year-old solitary kidney male patient with a history of laparoscopic right nephroureterectomy for high-grade urothelial carcinoma and rest of comorbidities are shown in Table 1. He initiated iHD presenting uremic symptoms and uncontrolled hypertension. He had a BMI of 36.3 kg/m², HbA1c level of 6.5%, and a urine albumin/creatinine ratio (UACR) of 4,200 mg/g and was being treated with linagliptin (5 mg/day), repaglinide (1.5 mg/day), and concomitant treatment with renin-angiotensin-aldosterone system inhibitors for the control of proteinuria. We discontinued both antidiabetic drugs and started semaglutide 0.25 mg once weekly. After 4 weeks, the dose of semaglutide was increased to 0.5 mg once weekly and after 8 weeks; the dose of 1 mg per week was prescribed, currently without changes. At 12 weeks, the UACR decreased to 3,244 mg/g (22.5% reduction) and an improvement in residual renal urea clearance (KrU) and creatinine clearance (CrCl) in 24 h from 4.4 to 9.5 and from 10 to 16 mL/min, respectively. Given the significant improvement in the GFR, we decided to add the use of sodium-glucose co-transporter type 2 inhibitor to the treatment, in light of their proven cardiorenal benefits. At 24 weeks, both CrCl and KrU remained unchanged, but UACR continued to decline to 2,924 mg/g, so we decided to discontinue renal replacement therapy (shown in Table 2).

Case 3
A 53-year-old morbidly obese, hypertensive, and diabetic woman had developed ESRD at the age of 45 years due to advanced nephroangiosclerosis and DKD. For 18 months, she underwent iHD with one session/week with a weight of 81.5 kg and a BMI of 33.9 kg/m² and HbA1c level of 7.1% and was treated with insulin degludec (10 U), repaglinide (3 mg/day),

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**Fig. 1.** Reduction of glycated HbA1c after starting once-weekly semaglutide (a). Changes in weight loss (b) fat (c) and lean mass (d) with respect to their baseline.
### Table 2. Evolution of dialysis parameters, residual renal function, and laboratory characteristics

#### Evolution of dialysis parameters

| Case | treatment duration | HDF (L) | KT (L) | V urea (L) | BP (mm Hg) | nPCR | IDWG (kg) |
|------|--------------------|---------|--------|------------|------------|------|-----------|
| 1    | 24 weeks           | 26,4    | 29     | 53         | 56         | 78   | 98        |
|      |                    | 170/79  | 139/70 | 1,53       | 1,36       | 0,8  | 1,6       |
| 2    | 24 weeks           | 25,1    | 25,6   | 53         | 60         | 85   | 84,5      |
|      |                    | 139/67  | 135/65 | 1,1        | 1,12       | 0,5  | 1,3       |
| 3    | 24 weeks           | 25,7    | 24,8   | 50         | 56         | 84   | 85        |
|      |                    | 158/86  | 125/75 | 0,85       | 1,06       | 0,8  | 0,5       |

#### Evolution of residual renal function parameters

| Case | urine urea (mg/dL) | KrU (mL/min) | MGFR mL/min | UACR (mg/g) | CrU/kg (mg/kg) | UU/kg (mg/kg) | CrCl (mL/min) |
|------|-------------------|--------------|-------------|------------|----------------|--------------|--------------|
| 1    | 436,4             | 738,7        | 5,84        | 10,9       | 16,5           | 256,3        | 16           |
|      |                    | 6,38         | 10,1        | 1,800      | 18,6           | 260,3        | 13.8         |
| 2    | 588,6             | 688,2        | 4,37        | 9,75       | 8,67           | 163,8        | 10           |
|      |                    | 4,37         | 9,75        | 2,900      | 8,65           | 161,4        | 16.4         |
| 3    | 692,8             | 675,9        | 4,33        | 5,06       | 8,82           | 116,6        | 4.7          |
|      |                    | 4,33         | 5,06        | 4,23       | 8,82           | 137,2        | 3.4          |

#### Evolution of laboratory characteristics

| Case | albumin (g/dl) | pre-albumin (mg/ml) | hb (g/dl) | blood glucose (mg/dl) | na (meq/l) |
|------|---------------|---------------------|-----------|-----------------------|-----------|
|      | pre           | post                | pre       | post                  | pre       |
| 1    | 3,89          | 3,44                | 27        | 29                    | 10,5      |
|      | 10,5          | 11,2                | 170       | 109                   | 143       |
| 2    | 3,5           | 3,55                | 26,05     | 25                    | 9,6       |
|      | 9,6           | 11                  | 186       | 142                   | 141       |
| 3    | 3,98          | 3,20                | 30,88     | 31,6                  | 11,1      |
|      | 11,1          | 10,6                | 150       | 115                   | 136       |

Wk, weeks; L, liters; HDF, convective volume hemodiafiltration; BP, blood pressure; nPCR, normalized protein catabolic rate; IDWG, interdialytic weight gain; V, volume, KrU, residual renal urea clearance; MGFR, mean glomerular filtration rate; UACR, urine albumin/creatinine ratio; CrU/Kg, excretion of creatinine normalized to kilogram; UU/kg, excretion of urea in urine normalized to kilogram; CrCl, creatinine clearance; Hb, hemoglobin; Na, sodium serum.
and linagliptin (5 mg/day) (shown in Table 1). Due to her BMI greater than 30, inclusion on the kidney transplant waiting list was restricted. We discontinued repaglinide and linagliptin and started semaglutide 0.25 mg once weekly. At 12 weeks, the dose of SC semaglutide was increased to 1 mg once weekly. At 24 weeks, the weight and BMI reduced to 71 kg and 29.5 kg/m², respectively. She did not present episodes of hypoglycemia, and insulin was suspended due to good glycemic control. Moreover, the patient is currently included in the kidney transplant program.

**Discussion**

In this report, we describe the efficacy, safety, and the favorable effects on glycemic control, lowering HbA1c, albuminuria, weight, blood pressure control, and preservation of residual kidney function (RKF) of SC semaglutide in 3 diabetic and obese patients with different clinical backgrounds who underwent iHD (1 session per week) during a 6-month follow-up. Only few randomized controlled studies have evaluated the safety and efficacy of the GLP-1RA, such as liraglutide (another long-acting GLP-1RA type), in dialysis patients [14, 15], and there are currently few case reports on the use of semaglutide in conventional hemodialysis [16]. To our best knowledge, this is the first case series in iHD and only one case report from our group, on the use of semaglutide with this hemodialysis regimen, can be found in the literature [17]. Recently, Aviles et al. [18] performed a multicenter, retrospective, observational study in patients with T2DM and CKD with an eGFR using CKD-EPI formula of >15 mL/min/1.73 m² and HbA1c between 7.5 and 9.5% treated with SC semaglutide for 12 months in real-world clinical practice. The main objectives were glycemic control as HbA1c < 7% and weight loss of >5%. 122 patients with eGFR: 50.32 ± 19.21 mL/min/1.73 m²; 54% had UACR: 30–300 mg/g and 20% UACR <30 mg/g were included. In this real-world study, the patients significantly improved glycemic control, decreased weight and albuminuria (by >50% in patients with macroalbuminuria). The administration of SC semaglutide in patients with DKD was safe and well tolerated.

GLP-1RA may exert a beneficial action on the renal metabolism which can be explained by its glomerular hemodynamic, tubular (natriuresis), and pleotropic effects [19, 20]. Mann et al. [21] performed a post hoc analysis of the SUSTAIN 1-7 clinical trials and analyzed the safety and effects on the renal function of SC once weekly semaglutide. They demonstrated that SC semaglutide exerted a protective renal effect as compared with placebo. Unlike sodium-glucose co-transporter type 2 inhibitor, GLP-1RA can be used in patients with advanced-stage CKD, the European Medicines Agency has approved the use of all commercially available human GLP-1 analogs up to a minimal eGFR of 15 mL/min/1.73 m² [10], owed mainly to the lack of clinical trials in DKD patients with stage 5 CKD in dialysis programs or kidney transplantation. Nevertheless, Marbury et al. [22] performed a multicenter, single-dose, open-label, parallel-group study with a sample size of 54 subjects, which were categorized into renal function groups (14 normal renal function a ten in each of the four renal impairment (RI) groups with mild, moderate, severe, and ESRD in hemodialysis). The patients received a single SC dose of semaglutide 0.5 mg. Semaglutide plasma concentrations were assessed <480 h post dose. The authors conclude that the semaglutide exposure in subjects with mild/moderate RI and ESRD was similar to that in subjects with normal renal function. The hemodialysis did not appear to affect the pharmacokinetics and tolerability of semaglutide, even with eGFR below 15 mL/min. PIONEER 5 studied the efficacy and safety of oral semaglutide (Rybelsus®) 14 mg versus placebo in patients with T2DM and moderate RI (eGFR, 30–59 mL/min/1.73 m²). In this trial, 60% of patients had an eGFR of 45 to less than 60 mL/min/1.73 m² and 40% had an eGFR of 30 to less than 45 mL/min/1.73 m². This trial demonstrated the efficacy and safety, including renal safety, were consistent with the GLP-1-RA class [23]. Additionally, there is currently a
dedicated kidney outcome trial for GLP-1RA (NCT03819153); the FLOW (Effect of Semaglutide vs. Placebo on the Progression of Renal Impairment in Subjects with Type 2 Diabetes and Chronic Kidney Disease) trial will evaluate whether semaglutide slows CKD progression in patients with T2DM. This phase 3 clinical trial includes more than 3,000 patients with T2DM and moderate-severe CKD (eGFR 25–75 mL/min/1.73 m² and UACR 300–5,000 mg/g). The primary endpoint is a compound episode renal failure defined by a decrease in eGFR ≥50%, ESRD, and death from renal causes or death from cardiovascular causes, and which is expected to end in 2024.

GLP-1RA have high glucose-lowering efficacy, although it varies within the drug class, reducing fasting glucose and HbA1c levels between 0.5 and 1.5%. The efficacy depends on dose, baseline HbA1c, and background therapy, as well as the chosen agent, being greater with those with a long half-life, such as semaglutide [9]. In our case series, the patients 1, 2 and 3 had a baseline HbA1c of 8.5, 6.5, and 7.1%, respectively. The action of semaglutide was associated with a reduction in HbA1c of 0.7–1% (shown in Fig. 1a). Patients 1 and 3 who were treated with insulin as they reached the dose of 1 mg/week of semaglutide in the 12 weeks, they were able to reduce (patient 1) or stop (patient 3) their usual doses of insulin. GLP-1RA are generally well tolerated and are associated with a low risk of hypoglycemia due to their glucose-dependent mode of action [24]. Hypoglycemia during dialysis can lead to greater cardiovascular risk and increased mortality [25]. Nevertheless, cardiovascular safety studies with GLP-1RA have shown no differences in hypoglycemia rates compared to placebo, except when associated with sulfonylureas or insulin. Moreover, this benefit was seen in patients with ESRD [26]. In our case series, after the introduction of semaglutide, the patients did not present hypoglycemic events.

Improvement of proteinuria was observed in the 3 patients. Showing a reduction of 15.1%, 30.9%, and 43.7% in the cases 3, 2, and 1, respectively (shown in Table 2). It is well known that the preservation of long-term RKF in dialysis patients is associated with lower morbidity and mortality, and one of the most relevant factors for its preservation is the reduction in urinary albumin excretion. Therefore, these drugs could delay the progression of ESKD and preserve RKF in patients on iHD and peritoneal dialysis. The reduction albuminuria is a consistent finding in previous studies with semaglutide [10, 27], as well as in a post hoc analysis of the SUSTAIN 1–7 trials [21]. In the SUSTAIN-6 trial, the UACR ratios at the end of treatment with respect to baseline were 0.973 with semaglutide 0.5 mg, 0.858 with semaglutide 1.0 mg, and 1.302 with the placebo [10]. SUSTAIN 1–5 and SUSTAIN 7 post hoc analyses showed a 30% reduction in albuminuria and also a regression to micro- or normoalbuminuria was observed in all degrees of albuminuria [21].

In our center, the hemodialysis regimen is adjusted according to RKF, considering an incremental regimen with a weekly session in patients with KrU >4 mL/min/1.73 m², as well as other criteria collected in the IHDIP study [28]. The 3 patients preserved CrCl and KrU after the introduction of GLP1-RA and one of them even improved their GFR, making it possible to discontinue hemodialysis. On the other hand, the mean GFR (semi-sum of KrU and CrCl) remained unchanged throughout the observed period. Nevertheless, in all cases, the KrU increased, and although the CrCl decreased in patients 1 and 3, the excretion of creatinine and urea in urine normalized to kilogram of weight was maintained in all 3 patients (shown in Table 2). Possibly the decrease in CrCl is due to the significant increase in lean mass and serum Cr in case 1 year 3.

It is also important to highlight weight loss with GLP-1RA, mainly as a consequence of a reduction in fat and not lean mass, which is maintained during long-term follow-up [29]. The three patients presented a reduction in fat mass measured by bioimpedance of 12, 20.6%, and 29.7% (patients 2, 1, and 3, respectively), while lean mass increased to 8.7%, 16.3%, and 23.1% with respect to their baseline (patients 2, 1, and 3, respectively) (shown in Fig. 1b, d). Despite the satiating effect of the drug, protein intake did not decline, as shown by the normalized protein catabolic rate > 1 g/kg per day in the 3 patients. On the other hand, the systolic blood pressure decreased by 18%, 3%, and 20% while diastolic blood pressure
decreased by 11.4%, 3%, and 12.8% in patients 1, 2, and 3, respectively. In the same way, the vast majority of sustain trials confirmed a significant reductions in blood pressure [21]. Lastly, the three patients presented good tolerance to the drug. A single patient presented transient nausea that subsided over time, without requiring treatment to be discontinued.

**Conclusion**

We found that GLP-1RA in diabetic and obese patients in iHD are safe and effective in achieving better glycemic control, weight, blood pressure, and other control goals that delay diabetic complications. All this could prevent albuminuria, maintain RKF, and produce an improvement in morbi-mortality. This may allow our patients to maintain a weekly hemodialysis session and facilitate their inclusion in the kidney transplant waiting lists.

**Statement of Ethics**

Ethical approval is not required for this study in accordance with local or national guidelines of our Ethics Committee of the Hospital Central Defensa Gomez Ulla. Patients have given their informed consent in writing to publish their cases (including the publication of images).

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare and the coauthors confirm their coauthorship of this manuscript.

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**Author Contributions**

José C. de la Flor, MD (primary author) conceived the ideas of the study; performed data collection, data analysis, and interpretation and provided revisions to scientific content of the manuscript. Javier Deira Lorenzo, PhD: provided revisions to scientific content of the manuscript and access to crucial research components. Alexander Marschall, MD: data analysis and interpretation and performed data collection. Francisco Valga, MD: provided revisions to scientific content of manuscript and performed data collection. Tania Monzón Vazquez, MD provided revisions to scientific content of the manuscript. Elisa Ruiz, MD provided revisions to scientific content of the manuscript and grammatical revisions to the manuscript.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. The data used to support the findings of this study are available from the corresponding author on request (Contact JDF, josedelaflor81@yahoo.com).
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