



ORIGINAL ARTICLE

# Semaglutide in type 2 diabetes with chronic kidney disease at high risk of progression—real-world clinical practice

Beatriz Aviles Bueno <sup>1</sup>, Maria Jose Soler <sup>2</sup>, Luis Perez-Belmonte<sup>3</sup>, Anabel Jimenez Millan<sup>4</sup>, Francisco Rivas Ruiz<sup>5</sup> and Maria Dolores Garcia de Lucas<sup>6</sup>

<sup>1</sup>Costa del Sol Hospital, Nephrology Department, Málaga, Spain, <sup>2</sup>Vall D'Hebron University Hospital, Nephrology Department, Universitat Autònoma de Barcelona, Barcelona, Spain, <sup>3</sup>Regional University Hospital and Biomedical Research Institute, Internal Medicine Department Málaga, Spain, <sup>4</sup>Puerto Real University Hospital, Endocrinology Department, Cádiz, Spain, <sup>5</sup>Costa del Sol Hospital, Internal Medicine Department, Málaga, Spain and <sup>6</sup>Research Unit, Marbella, Málaga, Spain

Correspondence to: Beatriz Aviles Bueno; E-mail: [avilesbb@hotmail.com](mailto:avilesbb@hotmail.com)

## ABSTRACT

**Background.** Semaglutide [glucagon-like peptide-1 receptor-agonist (GLP-1RA)] has shown nephroprotective effects in previous cardiovascular studies. However, its efficacy and safety in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) have been rarely studied.

**Methods.** This is a multicenter, retrospective, observational study in patients with T2D and CKD with glycosylated hemoglobin A1c (HbA1c) of 7.5–9.5% treated with subcutaneous semaglutide for 12 months in real-world clinical practice. The main objectives were glycemic control as HbA1c <7% and weight loss >5%.

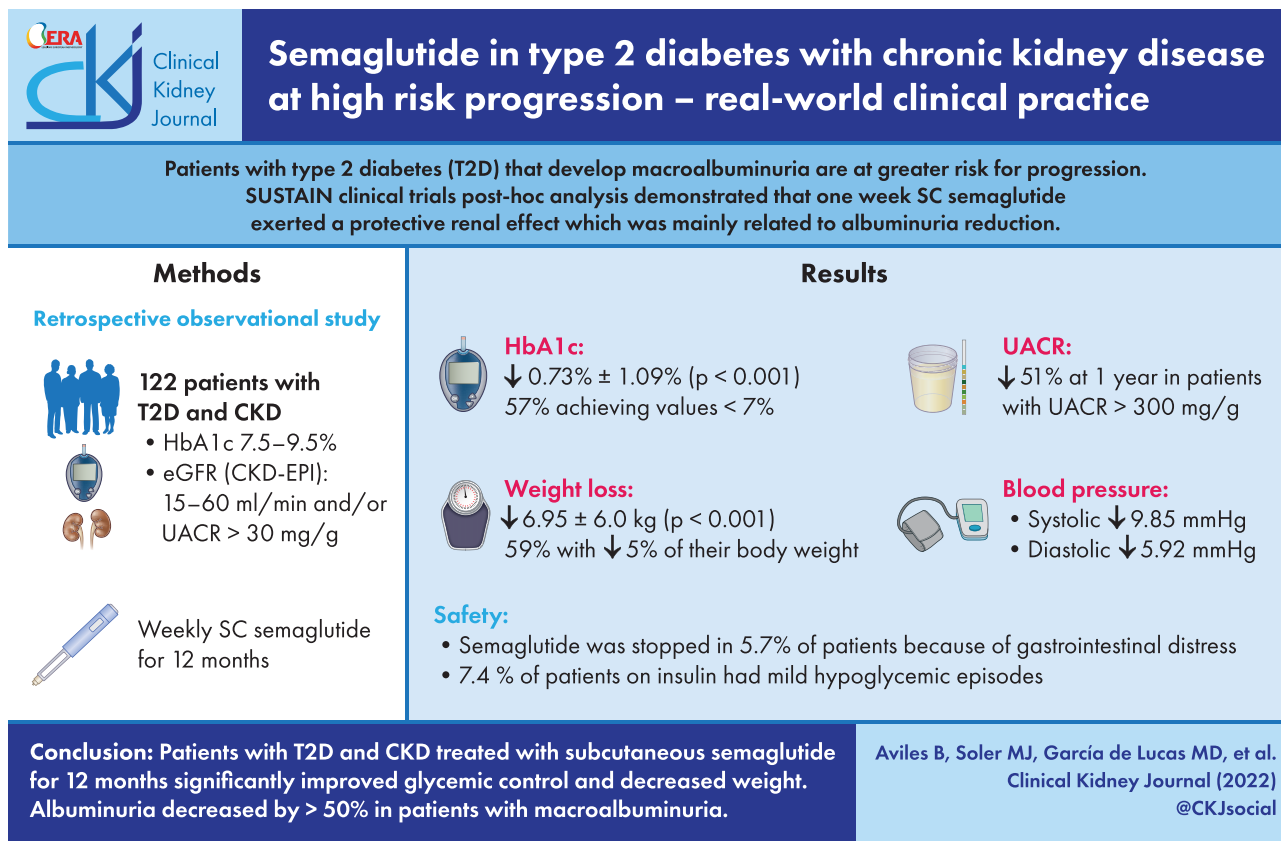
**Results.** We studied a total of 122 patients, ages  $65.50 \pm 11$  years, 62% men, duration of T2D 12 years, baseline HbA1c  $7.57\% \pm 1.36\%$  and an estimated glomerular filtration rate (eGFR)  $50.32 \pm 19.21$  mL/min/1.73 m<sup>2</sup>; 54% had a urinary albumin:creatinine ratio (UACR) of 30–300 mg/g and 20% had a UACR >300 mg/g. After 12 months of follow-up, HbA1c declined  $-0.73\% \pm 1.09\%$  ( $P < .001$ ), with 57% of patients achieving values <7% and weight loss of  $-6.95$  kg ( $P < .001$ ), with 59% of patients showing a reduction of >5% of their body weight. Systolic and diastolic blood pressure decreased  $-9.85$  mmHg and  $-5.92$  mmHg, respectively ( $P < .001$ ). The mean UACR decreased 51% in the group with baseline macroalbuminuria (UACR >300 mg/g). The mean eGFR (by the Chronic Kidney Disease Epidemiology Collaboration) remained stable. The need for basal insulin decreased 20% ( $P < .005$ ). Only 7% of patients on insulin had mild hypoglycemic episodes. Semaglutide was stopped in 5.7% of patients for digestive intolerance.

**Conclusions.** In this real-world study, patients with T2D and CKD treated with subcutaneous semaglutide for 12 months significantly improved glycemic control and decreased weight. Albuminuria decreased by >50% in patients with macroalbuminuria. The administration of GLP-1RA in patients with T2D and CKD was safe and well tolerated.

Received: 12.1.2022; Editorial decision: 28.2.2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

## GRAPHICAL ABSTRACT



**Keywords:** albuminuria, diabetic chronic disease, GLP-1RA, obesity, semaglutide

## INTRODUCTION

It is known that ~23–43% of patients with T2D develop chronic kidney disease (CKD) and currently diabetes is the first cause of end-stage kidney disease (ESKD) that require renal replacement therapy [1]. In addition, albuminuria appears early in the diagnosis of T2D in 17–26% of patients [2]. Patients with T2D and CKD who develop macroalbuminuria have a greater risk of cardiovascular disease mortality than progression to ESKD [3]. The Steno group, among others, have shown that intensified multifactorial intervention in type 2 diabetics with microalbuminuria, including a healthy lifestyle and early control of metabolic hyperglycemia, blood pressure (BP) and weight, slowed progression in nephropathy and renal function loss, reducing the risk of ESKD [4]. Furthermore, in the last decade it has been demonstrated that the use of drugs from classes such as renin-angiotensin-aldosterone system (RAAS) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) can delay or minimize micro- and macrovascular damage [5, 6].

Mann et al. [7] performed a post hoc analysis of the SUSTAIN 1–7 clinical trials and analyzed the safety and effects on the renal function of subcutaneous (SC) once-weekly semaglutide. They demonstrated that SC semaglutide exerted a protective renal effect as compared with placebo. Likewise, there was a greater reduction in the urinary albumin:creatinine ratio (UACR)

in those who presented with microalbuminuria (UACR 30–300 mg/g) and was strongest in patients with macroalbuminuria (UACR >300 mg/g) versus those with no presence of albuminuria [7, 8]. To date, the positive effects in terms of renoprotection exerted by semaglutide have been mainly related to albuminuria reduction.

To our knowledge, no real-world studies have been published on the use of semaglutide in patients with CKD. In the present study, our main objective was to evaluate the glycemic and renal efficacy and safety of semaglutide in patients with T2D and CKD over 12 months of follow-up.

## MATERIALS AND METHODS

This is a multicenter, retrospective, observational clinical study that was conducted at the departments of nephrology, internal medicine and endocrinology of three Spanish hospitals: the Costa del Sol Hospital in Marbella, Regional University Hospital of Málaga and the Puerto Real Hospital in Cádiz. The inclusion criteria were patients followed in clinics who are >18 years of age with T2D and an estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula of >15 mL/min/1.73 m<sup>2</sup>. Patients ≤18 years of age, with both eGFR (by CKD-EPI) >60 mL/min/1.73 m<sup>2</sup> and albuminuria <30 mg/g, kidney transplant, CKD stage 5 or patients taking part in clinical trials were excluded from the study.

The inclusion period was from May 2019 to January 2020 and patients were enrolled after signing the informed consent. We collected data at baseline and after 6 and 12 months  $\pm$  4 weeks from the beginning of treatment with SC semaglutide. A total of 122 patients with T2D and CKD, defined as an eGFR  $<$ 60 mL/min/1.73 m<sup>2</sup> and/or UACR  $>$ 30 mg/g were included in the study. All patients had previously received treatment with at least two oral and/or SC glucose-lowering agents. During follow-up visits, patients received guidance regarding a healthy lifestyle, such as eating a 1500-calorie diet and performing 120 min/week of aerobic exercise. In addition, antihypertensive and/or dyslipidemia treatment were intensified during the follow-up period when necessary. Patients had three or four follow-up appointments in the outpatient clinic. In the initial visit, semaglutide was started at a dose of 0.25 mg SC/week for 4 weeks. Then the dose was increased to 0.5 mg SC/week for 4 weeks and then 1 mg SC/week. The continuation of the treatment depended on the investigator's clinical judgement. Consecutive patients were included in the study after signing an informed consent form. The Ethical Committee of the Hospital Costa del Sol approved the study protocol [Ref FRR/RB (Cod 003\_dic\_PI-T2DCVRS/2019)].

The following data were obtained: anthropometric parameters [weight, body mass index (BMI), BP], cardiovascular risk factors, risk factors for micro and macrovascular complications and analytical parameters [fasting blood glucose, glycosylated hemoglobin A1c (HbA1c), lipid profile, eGFR (by the CKD-EPI equation); and UACR]. UACR was classified as microalbuminuria when values were 30–300 mg/g and macroalbuminuria when values were  $>$ 300 mg/g.

Hypoglycemic episodes were defined according to the American Diabetes Association criteria [9]. Cardiovascular events and other possible adverse drug effects were also collected. The main outcome variable was the percentage of patients who achieved good glucose control, defined as an HbA1c  $<$ 7% and weight loss  $>$ 5% of the total body weight, by the end of the study period. Secondary outcome variables included any changes in fasting blood glucose levels, BMI, BP, eGFR, UACR, hypoglycemic episodes, treatment withdrawal or a reduction in insulin units at the end of the study.

### Statistical analysis

A descriptive analysis was performed using measurements of central tendency, dispersion and position for quantitative variables and distribution of frequency for qualitative variables. A paired sample t-test was used for quantitative variables and McNemar's test for qualitative variables was used for studying differences between pairs. A generalized linear model was used to identify differences in quantitative variables in the baseline values versus values at 12 months. Statistical significance was established as  $P <$  .05. All statistical analyses were performed using SPSS version 19.0 software (IBM, Armonk, NY, USA).

## RESULTS

The clinical and epidemiological characteristics of the 122 patients included in our study are shown in Table 1. The mean age was  $65.56 \pm 11$  years, 62% were males and the mean duration of T2D was  $12.3 \pm 3.4$  years. The mean BMI was  $35.8 \pm 4.79$  kg/m<sup>2</sup>. Previous antidiabetic treatment included 50% receiving metformin, 42% SGLT2i, 66.4% on basal insulin and 27.8% on rapid-acting insulin. A total of 64.8% of all patients switched from another GLP-1RA (liraglutide, dulaglutide, exenatide LAR)

**Table 1. Clinical and epidemiological baseline data**

Characteristics	Values
Age (years), mean $\pm$ SD	65.50 $\pm$ 11
Male, n (%)	75 (62)
eGFR (CKD-EPI; mL/min/1.73 m <sup>2</sup> ), n (%)	
>60	
60–45	27 (22)
45–30	42 (34.4)
30–15	42 (34.4)
	11 (9)
UACR (mg/g), n (%)	
>300	24 (20)
30–300	66 (54)
<30	32 (26)
Basal insulin, n (%)	81 (66.4)
Rapid acting insulin, n (%)	34 (27.8)
Metformin, n (%)	61 (50)
DPP4i, n (%)	19 (15.6)
GLP-1RA switched, n (%)	79 (64.8)
Liraglutide	48 (39.3)
Dulaglutide	28 (23)
Exenatide LAR	3 (2.5)

DPP4i: dipeptidyl peptidase-4 inhibitor.

to semaglutide in the framework of this study. The majority (95.9%) of them were under renin–angiotensin system blockade.

Data on comorbidities and previous cardiovascular events are presented in Figure 1. Seventy-four percent presented micro- or macroalbuminuria. The mean UACR was  $349.5 \pm 863.2$  mg/g {median 78.5 mg/g [interquartile range (IQR) 26–199.5]} [20%,  $>$ 300 mg/g; 54%, 30–300 mg/g and 26%,  $<$ 30 mg/g]. The mean eGFR (by the CKD-EPI equation) was  $50.32 \pm 19.21$  mL/min/1.73 m<sup>2</sup>. The results after 12 months of treatment with once-weekly SC semaglutide are shown in Table 2. The mean HbA1c declined by  $-0.73 \pm 1.09\%$  (from  $7.57 \pm 1.36$  to  $6.83 \pm 0.85$ ;  $P <$  .001), with 57% of patients achieving the target of an HbA1c level of  $<$ 7%. Patients had a mean weight loss of  $-6.95 \pm 6.0$  kg (from  $98.48 \pm 16.6$  to  $91.53 \pm 16.42$ ;  $P <$  .001), with 59% of patients achieving the target of  $-5\%$  of total body weight. UACR declined by 53%, an average of  $-162.21 \pm 365.77$  mg/g [from  $349.49 \pm 863.2$  to  $187.28 \pm 897.39$ ;  $P <$  .001; median 78.5 mg/g (IQR 26–199.5) to 40 (6–103),  $P <$  .001]. By subgroups according to baseline albuminuria, we observed that the group with macroalbuminuria (UACR  $>$ 300 mg/g) presented a more significant albuminuria decrease at 6 and 12 months, 39% ( $P <$  .05) and 51% ( $P <$  .001), respectively (see Figure 2) and was the group with a higher percentage (58.3%) of T2D patients treated with SGT2i (see Table 3). Surprisingly, the greatest weight loss occurred in the group with microalbuminuria ( $-8.32 \pm 5.59$  kg,  $P <$  .01 in UACR 30–300 mg/g;  $-6.74 \pm 6.07$  kg,  $P <$  .01 in UACR  $>$ 300 mg/g; and  $-4.35 \pm 6.05$  kg,  $P <$  .01 in UACR  $<$ 30 mg/g).

The mean eGFR (by the CKD-EPI equation) remained stable, with a small nonsignificant increase of 2.2 mL/min/1.73 m<sup>2</sup>. Systolic and diastolic BP levels decreased by an average of  $9.85 \pm 13.34$  mmHg (from  $129.95 \pm 11.27$  to  $120.09 \pm 6.09$ ;  $P <$  .001) and  $5.92 \pm 7.43$  mmHg (from  $77.05 \pm 8.95$  to  $71.12 \pm 7.83$ ;  $P <$  .001), respectively. Low-density lipoprotein cholesterol and triglyceride levels decreased by  $10.79 \pm 28.21.1$  mg/dl ( $P <$  .001) and  $29.15$  mg/dl  $\pm$  91.47 ( $P <$  .001), respectively. Seven percent of patients on insulin had mild hypoglycemic episodes. The patients in this study decreased the need for basal and rapid-acting

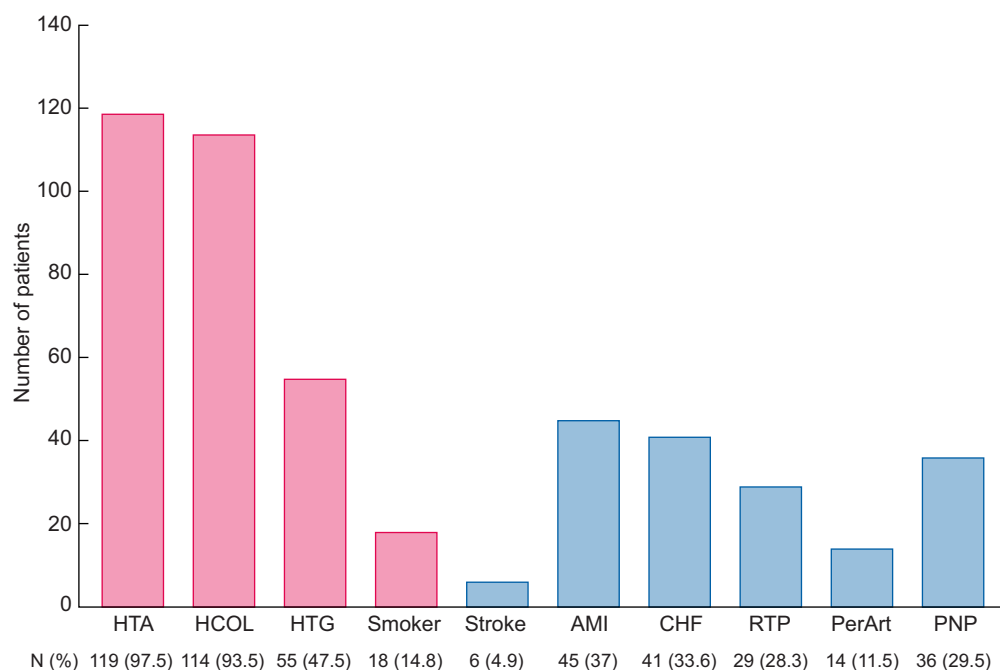


FIGURE 1: Previous patients comorbidity, risk factors and cardiovascular diseases N(%)

Table 2. Data at baseline and after 12 months of treatment with semaglutide

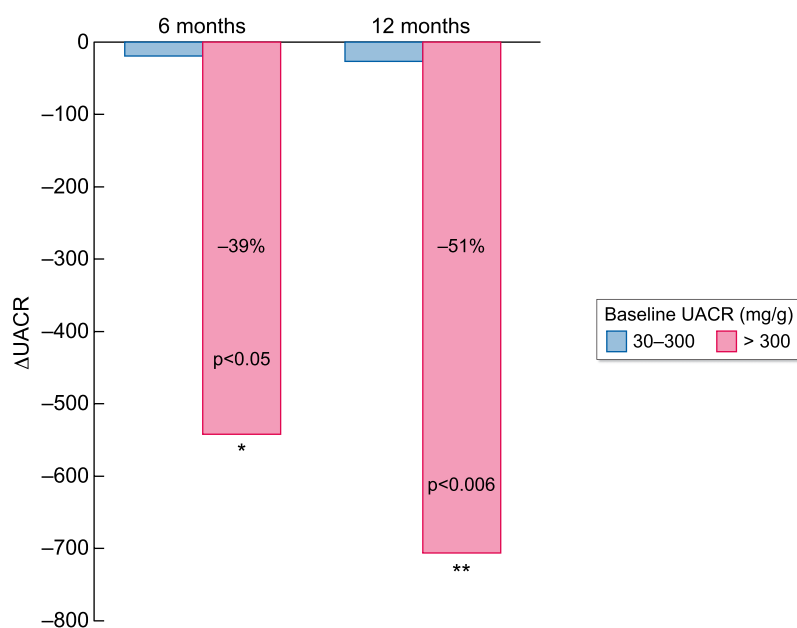
Characteristics	Baseline (n = 122)	12 months (n = 115)	Change after 12 months <sup>a</sup>	P-value
Glucose (mg/dl), mean ± SD	148 ± 52.44	122.84 ± 25.96	-25.95 ± 47.53	<.001
HbA1c (%), mean ± SD	7.57 ± 1.36	6.83 ± 0.85	-0.73 ± 1.09	<.001
Patients with HbA1c <7, n (%)	44 (36)	66 (57.4)		
Mild hypoglycemia, n (%)		9 (7.4)		
Basal insulin (IU), mean ± SD	44.19 ± 8.37	32.41 ± 8.98	-11.78 ± 15.17	<.005
Rapid-acting insulin (IU), mean ± SD	22.35 ± 9.35	14.58 ± 9.89	-7.77 ± 11.93	.43
Weight (kg), mean ± SD	98.72 ± 16.80	91.53 ± 16.42	-6.95 ± 6.00	<.001
BMI (kg/m <sup>2</sup> ), mean ± SD	35.8 ± 4.79	33.33 ± 4.77	-2.54 ± 2.22	<.001
Weight loss >5%, n(%)		68 (59)		
UACR (mg/g), mean ± SD	349.49 ± 863.16	187.28 ± 497.39	-162.21 ± 365.77	<.001
UACR (mg/g), median (Q1–Q3)	78.5 (26–199.5)	40 (6–103)		<.001
eGFR (CKD-EPI; mL/min/1.73 m <sup>2</sup> ), mean ± SD	50.32 ± 19.21	52.55 ± 19.26	2.2 ± 0.38	.07
Systolic BP (mmHg), mean ± SD	129.95 ± 11.27	120.09 ± 09	-9.85 ± 13.34	<.001
Diastolic BP (mmHg), mean ± SD	77.05 ± 8.95	71.12 ± 7.83	-5.92 ± 7.43	<.001
Hypertensive medications/patient, n (%)	1.61 (98.4)	1.49 (95.9)		
RAS blockade, n (%)	117 (95.9)	115 (95)		
LDL cholesterol (mg/dl), mean ± SD	80.47 ± 32.50	69.68 ± 23.67	-10.79 ± 28.21	<.001
TG (mg/dl), mean ± SD	190.67 ± 113.20	161.51 ± 94.76	-29.15 ± 91.47	.001
Lipid-lowering medications/patients, n	1.0	1.06		
Statins, <sup>b</sup> n (%)	116 (95.1)	120 (98.4)		
Fibrates	28 (22.9)	20 (17.4)		
Semaglutide withdrawal, n (%)		7 (5.7)		

Q1: quartile 1; Q3: quartile 3; LDL: low-density lipoprotein; TG: triglycerides.

<sup>a</sup>Final-initial.<sup>b</sup>Includes ezetimibe.

insulin by 20.25% [-11.78 IU (95% CI 8.02–15.74; P < .005)] and 23% [-7.77 IU (95% CI 0.56–14.97; P = ns)], respectively. Semaglutide was suspended in 5.7% of cases; 65% of these suspensions were due to digestive intolerance. Nausea (1.6%) and vomiting

(0.8%) were the most frequent digestive problems, followed by constipation (0.8%) and diarrhea (0.6%). Weight loss failure was the second most common reason to stop semaglutide in 30% of the cases and in 5% it was by patient decision.



	Baseline	6 months	Δ6 months	12 months	Δ12 months
<b>UACR 30–300 mg/g:</b>					
Mean (SD)	95.2 (61.84)	75.96 (78.06)	-19.24 (74,33)	68.55 (134.41)	-26.66 (126.80)
Median (Q1–Q3)	82.5 (43–124)	55 (28–66.2)		40 (22.5–61.5)	
<b>UACR &gt;300 mg/g:</b>					
Mean (SD)	1393 (1460.62)	850.25 (955)	-542.75 (809.54)*	686.08 (902.67)	-706.61 (1132.01)**
Median (Q1–Q3)	985 (413.2–1705)	329 (169–1164)		267 (150–672)	

FIGURE 2: Effect of semaglutide treatment on albuminuria: UACR after 6 and 12 months of treatment with semaglutide as compared with baseline. \*P < .05; \*\*P < .006. Q1: quartile 1; Q3: quartile 3.

## DISCUSSION

In recent years, SGLT2i and GLP-1RA have been associated with improved cardiovascular and kidney outcomes. GLP-1RA could be used for adequate glucose control in multiple stages of diabetic kidney chronic disease (DKD) without an increased risk of hypoglycemia and with additional benefits in terms of weight reduction, cardiovascular outcomes and kidney outcomes [10, 11]. On the other hand, sulfonylureas, insulin or repaglinide increase the risk of hypoglycemic episodes and metformin has been associated with lactic acidosis [12–14]. Epidemiological data support the relationship between glucose control and nephropathy in diabetes [15]. However, a major challenge in the management of DKD is the increased risk of hypoglycemia. Therefore, careful individualized glucose control, medication prescription, patient education, therapeutic planning and vigilance for hypoglycemia are all important components in the management of patients with DKD. The Kidney Disease: Improving Global Outcomes guidelines in DKD recommend individualizing HbA1c targets, ranging from <6.5% to <8.0% in patients not treated with dialysis. Safe achievement of lower HbA1c targets (<6.5% or <7.0%) may be facilitated by selection of antihyperglycemic agents that are not associated with hypoglycemia [15, 16]. The GLP-1RA liraglutide [17, 18], dulaglutide [19] and SC semaglutide have been shown to improve glucose control in DKD patients with an eGFR >15 mL/min/1.73 m<sup>2</sup> and oral semaglutide [20, 21] with an eGFR >30 mL/min/1.73 m<sup>2</sup>.

Liraglutide obtained better glucose control and weight reduction, with lower hypoglycemia risk compared with placebo [22]. In the PIONEER 5 trial, once-daily oral semaglutide 14 mg was superior to placebo in decreasing HbA1c and body weight in DKD patients with an eGFR of 30–59 mL/min/1.73 m<sup>2</sup>, with few hypoglycemic episodes [23]. In our study, 57% of patients reached an HbA1c <7% with a significant 20% decrease in basal insulin needs, and 7% of patients had mild hypoglycemic episodes. Therefore we safely ameliorated glucose control in our DKD patients by reducing the risk of hypoglycemia.

In the LEADER trial [17–24], patients with an eGFR >15 mL/min/1.73 m<sup>2</sup> were included, 23% of them had an eGFR <60 mL/min/1.73 m<sup>2</sup>, 36% had albuminuria >30 mg/g and 10% had albuminuria >300 mg/g. Liraglutide decreased by 22% the risk of a secondary composite kidney endpoint (new-onset macroalbuminuria, sustained serum creatinine duplication, initiation of RRT or renal death). This benefit was mainly at the expense of macroalbuminuria reduction. Furthermore, in the SUSTAIN 6 trial [20] they also included patients with an eGFR >15 mL/min/1.73 m<sup>2</sup>, 28.5% of them had an eGFR <60 mL/min/1.73 m<sup>2</sup> and 12.7% had baseline macroalbuminuria. SC semaglutide showed a 36% risk reduction in a secondary combined kidney endpoint (new-onset macroalbuminuria, doubling serum creatinine reaching an eGFR <45 mL/min/1.73 m<sup>2</sup>, initiation of renal replacement therapy or renal death). The renal benefit was mainly related to the treatment impact on new-onset macroalbuminuria (2.7% in the semaglutide group versus 4.9% in the



**Table 3. Baseline and changes in oral antidiabetic, antihypertensive and dyslipidemia medication according to basal albuminuria category**

Medication by baseline UACR	Baseline, n (%)	24 months, n (%)
<b>SGLT2i (mg/g)</b>	<b>52 (42.6)</b>	<b>56 (45.9)</b>
>300	13 (54.2)	14 (58.3)
30–300	26 (39.4)	29 (43.9)
<30	13 (40.6)	13 (40.6)
<b>Metformin (mg/g)</b>	<b>61 (50)</b>	<b>44 (36.1)</b>
>300	10 (41.7)	7 (29.2)
30–300	37 (56.1)	31 (47)
<30	14 (43.8)	6 (18.8)
<b>DPP4i (mg/g)</b>	<b>19 (15.6)</b>	<b>0</b>
>300	1 (4.2)	
30–300	11 (16.7)	
<30	7 (21.9)	
<b>Pioglitazone (mg/g)</b>	<b>1 (0.8)</b>	<b>2 (1.7)</b>
>300	0	1 (4.2)
30–300	0	0
<30	1 (3.1)	1 (3.1)
<b>anti-HTA (mg/g)</b>	<b>120 (98.4)</b>	<b>117 (95.9)</b>
>300	23 (95.8)	23 (95.8)
30–300	65 (98.5)	65 (98.5)
<30	32 (100)	29 (90.6)
<b>RASi (mg/g)</b>	<b>117 (95.9)</b>	<b>116 (95.1)</b>
>300	23 (95.8)	23 (95.8)
30–300	64 (97.5)	64 (97.5)
<30	31 (98.5)	30 (97.4)
<b>Statins<sup>a</sup> (mg/g)</b>	<b>116 (95.1)</b>	<b>120 (98.4)</b>
>300	23 (95.8)	24 (100)
30–300	63 (95.5)	65 (98.5)
<30	30 (93.8)	31 (96.9)

anti-HTA: antihypertensive medication (includes  $\beta$ -blockers, calcium channel blockers,  $\alpha$ -blockers, mineralocorticoid agonists and diuretics); DPP4i, dipeptidylpeptidase-4 inhibitor; RASi: renin-angiotensin system inhibitor. <sup>a</sup>Includes ezetimibe.

placebo group;  $P = .001$ ). Post hoc pooled analyses of LEADER and SUSTAIN 6 showed a 30% reduction in albuminuria and that regression to micro- or normoalbuminuria occurred for all degrees of albuminuria in patients treated with semaglutide [25]. In the same way the subanalysis confirmed a significantly milder eGFR decline with 1 mg SC semaglutide in patients with baseline eGFR between 30 and 60 mL/min/1.73 m<sup>2</sup> [2–26]. Liraglutide or semaglutide are small-sized GLP-1RAs that are able to cross the blood–brain barrier and reach satiety centers. Therefore a greater effect on body weight has been seen in clinical trials with them than with large-sized GLP-1RAs such as dulaglutide and albiglutide [27]. In our study, 56% of patients were switched from another GLP-1RA to semaglutide (64.8% from liraglutide, 31% dulaglutide and 3.2% exenatide-LAR). The most frequent indication for the change was failure to lose weight with the previous GLP-1RA. In mice, it has been shown that semaglutide accesses and activates regions of the brain involved in reward behavior and food intake [28]. In SUSTAIN 10, SUSTAIN 7 and SUSTAIN 3, semaglutide has been the more powerful molecule to lower body weight compared with liraglutide, dulaglutide and exenatide, respectively [29–31]. In our study, patients decreased total body weight by >5% in 59% of the population. However, by subgroups, it is not the patients with greater reductions in albuminuria where we find the greatest weight loss. We hypoth-

esize that the effect of semaglutide in the decrease of albuminuria could be more related to direct renal mechanisms than to indirect ones such weight loss, glucose or BP control. Moreover, the GLP1-ARs exert their nephroprotective effect by indirect and direct mechanisms. It seems that the local or receptor-mediated mechanisms on the kidney are responsible for >60% of the kidney benefit. In the LEADER study, the difference in kidney outcome was not altered by adjustment for a change in glucose control, body weight or systolic BP (indirect mechanisms) [17]. Experimental data demonstrated that the improvements in renal outcomes may be ascribed in part to the anti-inflammatory antioxidative and hemodynamic properties of the GLP1-RAs [32].

In our study, mean systolic and diastolic BP decreased by an average of  $9.85 \pm 13.34$  mmHg (from  $129.95 \pm 11.27$  to  $120.09 \pm 6.09$ ;  $P < .001$ ) and  $5.92 \pm 7.43$  mmHg (from  $77.05 \pm 8.95$  to  $71.12 \pm 7.83$ ;  $P < .001$ ), respectively. These decreases are greater than in SUSTAIN 6 [20], where the mean systolic BP decreased 3.4 and 5.4 mmHg among those receiving 0.5 and 1.0 mg of SC semaglutide, respectively. In other SUSTAIN trails, SC semaglutide was generally associated with reductions in systolic BP that achieved statistical significance (except for SUSTAIN 1, 7 and 10) [31, 33–36]. Diastolic BP was generally reduced, but differences were not significant versus comparators. In our study, weight loss may have contributed to better BP control. Interestingly, 72% of our patients were at high risk of CKD progression with micro- or macroalbuminuria [mean for all the patients  $349 \pm 843$  mg/g; median 78.5 (IQR 26–199.5)]. In addition, between 30 and 40% already have an underlying cardiovascular disease. The positive effect of semaglutide in terms of decreasing albuminuria may suggest a delay in progression toward ESKD; however, we were unable to demonstrate a positive effect in terms of eGFR delay. The lack of this positive effect may be related to the small sample size and the short-term follow-up. In post hoc pooled analysis from SUSTAIN 6 and PIONEER 6 of SC and oral semaglutide, respectively [37], in 6480 subjects, researchers observed an annual rate of eGFR change of 0.60 mL/min/1.73 m<sup>2</sup> (95% CI 0.31–0.90;  $P < .0001$ ) lower with semaglutide compared with placebo in the first year estimated to treatment difference (ETD). Specifically in the subgroup with an eGFR  $\geq 30$ –<60 mL/min/1.73 m<sup>2</sup> at baseline, the ETD for semaglutide versus placebo was 1.07 mL/min/1.73 m<sup>2</sup>/year (95% CI 0.46–1.68;  $P < .01$ ). The authors conclude that although benefits were observed in the overall population, the findings indicate that the primary benefit may be observed in those with established CKD. To date, there are no published GLP-1RA trials with a primary endpoint of kidney events or enrolling only DKD patients. Although real-life studies tend to obtain poorer results than clinical trials, the positive results achieved in this study may be explained in part by good therapeutic compliance, which was possibly related to a higher frequency of visits.

One of the main limitations of our study is that the design was uncontrolled and there were multiple interventions concomitant with semaglutide treatment. Also, the existence of modifications in the individual behavior of patients in response to their awareness of being observed cannot be ruled out. In addition, this was an exploratory analysis and its results must be interpreted with caution. Currently there is an ongoing randomized clinical trial, the FLOW trial [A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease (FLOW) (NCT03819153)], is assessing the impact of semaglutide on primary kidney outcomes in DKD.

In conclusion, in real-life clinical practice, 12 months of treatment with SC semaglutide in patients with T2D and CKD at high risk of progression ameliorates metabolic control and weight. Furthermore, we also demonstrated a reduction in albuminuria of >50% in the population with macroalbuminuria, improved BP and lipid control with a decrease in insulin needs.

## ACKNOWLEDGEMENTS

The authors would like to thank the Costa del Sol Hospital Research Unit for its contributions to this work.

## FUNDING

This research received no external funding.

## CONFLICT OF INTEREST STATEMENT

B.A.B. has received speaker honoraria from Novo Nordisk, Boehringer Ingelheim and AstraZeneca. M.J.S. has received speaker honoraria and has served on advisory boards for Novo Nordisk, Jansen, Boehringer Ingelheim, Mundipharma, Eli Lilly, AstraZeneca, Vifor Fresenius Medical Care, ICU Medical, Bayer, GE Healthcare and Travere. M.J.S. is the Editor-in-Chief Elect of CKJ. L.M.P.-B. has received consulting fees and honoraria for membership on advisory boards from Novo Nordisk, Janssen, Boehringer Ingelheim, Eli Lilly, AstraZeneca, Novartis, Fresenius, Abbott and Sanofi. A.I.J.M. has received speaker honoraria from Novo Nordisk, Mundipharma, AstraZeneca and Boehringer Ingelheim and has served as a consultant for NovoNordisk. M.D.G.d.L. has served as a consultant for Novo Nordisk, Boehringer Ingelheim, Mundipharma and AstraZeneca and has received speaker honoraria from Novo Nordisk, Boehringer Ingelheim, Mundipharma, Eli Lilly, AstraZeneca and Novartis. None of these financial contributions are related to this manuscript.

## REFERENCES

- Martinez Martinez-Castelao A, Soler MJ, Navarro-González JF et al. Will the new molecules be effective in renal and cardiovascular protection in diabetes mellitus and diabetic kidney disease. *Nefrologia* 2019; **39**: 3–10
- Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease. *Clin J Am Soc Nephrol* 2017; **12**: 2032–2045
- Afkarian M, Sachs MC, Kestenbaum B et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013; **24**: 302–308
- Oellgaard J, Gæde P, Rossing P et al. Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits. *Kidney Int* 2017; **91**: 982–988
- Magee C, Grieve DJ, Watson CJ et al. Diabetic nephropathy: a tangled web to unweave. *Cardiovasc Drugs Ther* 2017; **31**: 579–592
- Zoungas S, Arima H, Gerstein HC 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**: 431–437
- Mann J, Hansen T, Idorn T 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. *Lancet Diabetes Endocrinol* 2020; **8**: 880–893
- Marso SP, Bain SC, Consoli A et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375**: 1834–1844
- American Diabetes Association. Standards of medical care in diabetes—2018. *Diab Care* 2018; **41**(Suppl 1): S1–S159
- Fernandez-Fernandez B, Fernandez-Prado R, Górriz J et al. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation and Study of Diabetic Nephropathy with Atrasentan: what was learned about the treatment of diabetic kidney disease with canagliflozin and atrasentan? *Clin Kidney J* 2019; **12**: 313–321
- Sarafidis P, Ferro CJ, Morales E et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECAm and the DIABESITY working groups of the ERA-EDTA. *Nephrol Dial Transplant* 2019; **34**: 208–230
- Ginsberg JS, Zhan M, Diamantidis CJ et al. Patient-reported and actionable safety events in CKD. *J Am Soc Nephrol* 2014; **25**: 1564–1573
- Farrington K, Covic A, Nistor I et al. Clinical practice guideline on management of older patients with chronic kidney disease stage 3b or higher (eGFR <45 mL/min/1.73 m<sup>2</sup>): A summary document from the European Renal Best Practice Group. *Nephrol Dial Transplant* 2017; **32**: 9–16
- Martínez-Castelao A, Górriz JL, Ortiz A et al. ERBP guideline on management of patients with diabetes and chronic kidney disease stage 3B or higher. Metformin for all? *Nefrologia* 2017; **37**: 567–571
- Shurraw S, Hemmelgarn B, Lin M et al. Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. *Arch Intern Med* 2011; **171**: 1920–1927
- Perkovic V, Agarwal R, Fioretto P et al. Management of patients with diabetes and CKD: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. *Kidney Int* 2016; **90**: 1175–1183
- Mann JFE, Brown-Frandsen K, Marso SP et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017; **31**: 839–848
- Kapitza C, Nosek L, Jensen L et al. Semaglutide, a once-weekly human GLP-1 analog, does not reduce the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel. *J Clin Pharmacol* 2015; **55**: 497–504
- Gerstein HC, Colhoun HM, Dagenais GR et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; **394**: 121–130
- Marso SP, Bain SC, Consoli A et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375**: 1834–1844
- Mosenzon O, Blicher TM, Rosenlund S et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. *Lancet Diabetes Endocrinol* 2019; **7**: 515–527
- Davies MJ, Bain SC, Atkin SL et al. Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate

- Renal Impairment (LIRA-RENAL): a randomized clinical trial. *Diabetes Care* 2015; **39**: 222–230
23. Pfeffer MA, Claggett B, Diaz R et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015; **373**: 2247–2257
  24. Marso SP, Daniels GH, Brown-Frandsen K et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375**: 311–322
  25. Perkovic V, Bain S, Bakris G et al. FP483 Effects of semaglutide and liraglutide on urinary albumin-to-creatinine ratio (UACR)—a pooled analysis of the SUSTAIN 6 and LEADER trials. *Proceedings of the 56th ERAEDTA Congress, Budapest, Hungary, 13–16 June 2019*
  26. Perkovic V, Bain S, Bakris G et al. F482 Effect of GLP-1 analogue treatment on eGFR slope — data from SUSTAIN 6 and LEADER. Additional Analysis. *Proceedings of the 56th ERAEDTA Congress, Budapest, Hungary, 13–16 June 2019*
  27. Gorgojo-Martínez JJ. [New glucose-lowering drugs for reducing cardiovascular risk in patients with type 2 diabetes mellitus]. *Hipertens Riesgo Vasc* 2019; **36**: 145–161
  28. Jensen CB, Secher A, Hecksher-Sorensen J et al. Quantification of semaglutide distribution and action in mouse brain regions associated with reward and food intake. *Diabetes* 2017; **66**: A305
  29. Capehorn M, Cararig AM, Furberg JK et al. Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1–3 oral anti-diabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab* 2020; **46**: 100–109
  30. Pradley R, Aroda V, Lingvay I et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 2018; **6**: 275–286
  31. Ahmann A, Capehorn M, Charpentier G et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open label, randomized clinical trial. *Diabetes Care* 2018; **41**: 258–266
  32. Pyke C, Heller RS, Kirk RK et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology* 2014; **155**: 1280–1290
  33. Ahrén B, Masmiquel L, Kumar H et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol* 2017; **5**: 341–354
  34. Aroda VR, Bain SC, Cariou B. et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol.* 2017; **5**: 355–366
  35. Rodbard HW, Lidgway I, Reed J et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. *J Clin Endocrinol Metab.* 2018; **103**: 2291–2301
  36. Zinman B, Bhosekar V, Busch R. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol.* 2019; **7**: 356–367
  37. Tuttle K, Cherney D, Hadjadi S et al. TO002 Reduction in the rate of eGFR decline with semaglutide vs placebo: a post hoc pooled analysis of SUSTAIN 6 and PIONEER 6. *Nephrol Dial Transplant* 2020; **35(Suppl 3)**: gfaa141.TO002