Dulaglutide preserves kidney function and maintains metabolic control at a 36-month follow-up

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Abstract

The renal benefits of glucagon-like peptide-1 receptor agonists (GLP-1 RA) are based mainly on preservation of glomerular filtration and a reduction in macroalbuminuria. In controlled studies dulaglutide has shown good metabolic rate and slows the progression of glomerular filtration rate (GFR) loss. We analyzed, the metabolic control, the renal preservation data based on estimated GFR (eGFR) and the relationship of eGFR changes with baseline values at 36 months (M) follow–up. The results shows: glycated hemoglobin was reduced -1.4% at 12M, ($p<0.001$), fasting blood glucose showed a significant reduction (-30 mg/dL) at 12M ($p=0.005$), weight showed a 3.6 kg reduction at 12M ($p=0.009$). GFR did not show a worsening during follow-up: baseline value was 88.10±26.47 ml/min/1.73m2 and remained stable (83.25±29.27 ml/min/1.73m2; $p=0.134$) at the end of the study. Based on the 36M follow-up results, dulaglutide was shown to be an effective and nephroprotective drug in diabetic patients.

Introduction

Diabetes mellitus (DM) is a serious health problem that has reached alarming proportions, afflicting almost 500 million people worldwide in 2019.[1] Of the afflicted people, almost 40% will present with diabetic nephropathy at some point during the evolution of the disease. New drugs for treating DM, which demonstrate both cardiovascular and kidney benefits, have appeared in recent years. These drugs consist of glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium glucose luminal transport type 2 inhibitors (SGLT2i).[2,3] The mechanism by which these drugs cause kidney benefits appear to be multiple and are not entirely understood. On one hand they most likely would be related to weight reduction, blood pressure reduction or glycemic control.[4] Other mechanisms could include anti-inflammatory, anti-arteriosclerotic, and intrarenal mechanisms, such as natriuresis, activation of tubuloglomerular feedback and/or inactivation of the renin-angiotensin system (RAAS).[5,6]

The renal benefits of GLP-1 RA are based mainly on preservation of glomerular filtration and a reduction in macroalbuminuria.[3] Dulaglutide is a GLP-1 RA agonist with a long half-life. In the REWIND cardiovascular

safety trial of almost 10,000 patients in which dulaglutide was compared versus \soutplacebo for 5.2 years, a decrease in estimated glomerular filtration rates (eGFR) of 40% to 50% was demonstrated.[7] The AWARD-7 trial compared dulaglutide to insulin glargine in patients with type 2 DM (T2DM) and moderate–severe renal failure (mean eGFR=38 ml/min/m^2). [8] At 52 weeks of treatment, the dulaglutide group had a lower eGFR drop than the insulin group; the mean eGFR decline was -5.5 ml/min/1.73 m^2in the insulin glargine group compared with -0.7 for and -0.50 ml/min /1.73 m^2 for the 0.75 and 1.5 mg dulaglutide groups, respectively. In a real-life study over the course of a year, the initiation of insulin glargine versus dulaglutide treatment was compared in a patient base very similar to that in the AWARD-7 trial. The dulaglutide group demonstrated a significant decrease in eGFR (<30%) at one year of treatment. [9]

Our group has recently presented real-life data over two years with dulaglutide in a Spanish patient population.[10] The present study analyze renal function data based on eGFR in a subgroup of patients and to analyze the relationship between eGFR changes and their baseline values.

*Methods*Study design designed an observational, retrospective, multicenter study in patients with T2DM. Patients were enrolled from three different health areas: (1) San Carlos Clinical Hospital of Madrid; (2) University Hospital of Salamanca; and (3) two districts of Huelva, Huelva-Costa and Condado-Campiña. criteria consisted of several criteria: (1) patients >18 years with a diagnosis of DM2 and (2) receiving dulaglutide treatment at a weekly dose of 1.5 mg with no interruptions in treatment with this drug for at least 36 months (M) between December 2015 and December 2019 based on electronic prescriptions and a medical records review. Patients who did not fulfill these criteria were excluded. primary endpoint was evaluation of dulaglutide efficacy with respect to eGFR preservation in patients receiving dulaglutide treatment for 36M. To measure this parameter, eGFR was analyzed at baseline and 12, 24, and 36M after starting the drug. eGFR evaluation (measured by MDRD-4[11]) differences according to antidiabetic treatment was the secondary endpoint. Other endpoints were changes/improvements in fasting blood glucose, glycosylated hemoglobin (HbA1c), and weight at the end of the study. Analyzed variables included age, gender, eGFR, fasting blood glucose, HbA1c, weight, and antidiabetic treatment at study initiation. The study received the approval of the ethics committee of the study reference center and was in compliance with the Helsinki declaration. Every modification in the management of the patients was decided by the treating physician.

Results:

Among the 147 patients who reached 24M of dulaglutide treatment in our previous study,11 we selected a cohort of those had reached 36M with an active prescription of dulaglutide. 52 of those were excluded because they did not meet the inclusion criteria. Of the 95 initial patients, we recorded eight drop-outs due to several causes (8.42%): (1) four due to change of GLP-1 RA; (2) one death; (3) gastrointestinal side effects in one and (4) two for unspecified causes.

Demographic and baseline characteristics

Mean age of the subjects included in the study was 57.88±9.96 years, and most of them were women (60.93%). More than 80% had received previous antidiabetic treatment with metformin and insulin, which were the most frequently used agents. Baseline values are shown in Table 1.

Primary and secondary endpoints

During the follow-up, eGFR (primary endpoint) did not show a statistically significant worsening over the course of the study. The baseline value was 88.10±26.47 ml/min/1.73m^2 and remained stable (83.25±29.27 ml/min/1.73m^2; p=0.134) until the end of the study at 36M. Values during follow-up are shown in Table 2.

The secondary endpoint includes results based on the type of oral antidiabetic drug (metformin, sulfonylureas, dipeptidyl peptidades-4 inhibitors [DPP-4i], and SGLT2i) that patients were taking. In this case, we did not observe eGFR differences during the follow-up, except in the insulin group. Patients using insulin had a worse GFR at 12M (p=0.008) that those who did not (Table 3).

Methabolic changes

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HbA1c was significantly reduced by -1.4% at 12M and this reduction was maintained at 24 and 36M in the dulaglutide group (p<0.001). Similarly, fasting blood glucose levels showed significant reductions (-30 mg/dL) at 12M (p=0.005) and this reduction was also maintained until 24 and 36M follow-up. Weight showed a trend comparable to glucose levels. In the first 12M, the reduction was 3.6 kg (p=0.009), which remained unchanged at 36M (Table 2).

DiscussionOur results show for the first time, based on a real-life long-term follow-up study, that dulaglutide is an effective and nephroprotective drug for the treatment of patients with T2DM. It also allows an excellent metabolic control.

Despite optimal lifestyles, blood glucose, and hypertension management and/or the use of modular RAAS pathway drugs, the residual risk for kidney disease remains high in diabetic patients.[12]The annual loss of glomerular filtration rate (GFR) in patients with T2DM has been estimated at 5.2 +- 4.1 ml/min/1.73m^2.[13] An intense search for drugs that can decrease this residual risk and prevent development of diabetes- and/or non-diabetes-related CKD is ongoing. Nephroprotection is among the many metabolic and cardiovascular benefits of the new drugs for diabetes, SGLT2i and GLP-1 RA. These mechanisms are not entirely understood and depend on various mechanisms.

In pivotal studies, dulaglutide has been shown to prevent diabetic kidney disease (DKD) in pivotal clinical trials and in real-life situations. [7–9] In the current study at one year of treatment, patients who received dulaglutide had a lower decrease in eGFR than those who received insulin glargine (specifically -0.4 versus -0.9 mL/min/1.73 m^2; p=0.0024). These values were based on an eGFR of 84.4+-23.4 mL/min/1.73m^2. Patients had a mean age of 59.5+-10.9, HbA1c 8.2+-1.7%, and were taking drugs that influenced the RAAS pathway by about 45%. Our work is novel in that it extends over 36M of treatment and confirms these previous findings. We started from a baseline eGFR of 88.1+-26.47 mL/min/1.73m^2 as calculated with the MDRD-4 formula, a mean age of 57.8+-9.96, and an HbA1c 8.53+-1.91%. Most of them (80%) received treatment with drugs that influenced the RAAS pathway.

It can be seen that in metabolic T2DM, baseline HbA1c levels decreased during the first year by 1.4%, levels that were maintained throughout the follow-up period and were comparable to the reduction observed in other studies. Regarding the maintenance of renal function, it can be observed that the eGFR was maintained in the overall number of patients in addition to the analysis of subgroups with concomitant treatments. We used the age-related decrease in GFR as a reference, which allowed us to observe that in the patients in our study, the loss of GFR was less than expected compared to the age-related value without considering the associated pathologies. In our study, the overall number of patients had a mean eGFR decrease of -4.85/mL/min/1.73m^2 at 36M, which in a population with T2DM, could be compared to -15.6 mL/min /1.73m^2 for the same time.[13] In the subgroup analysis, we found that in the group in which patients received insulin, this drop in eGFR was more significantly pronounced at 36M than in the group without insulin (-5.39 versus -3.36 ml/min/1.73m^2; p=0.006) as shown in Table 2. In the insulin subgroup, they started from a mean HbA1c value of 1% higher (8.87%+-1.97% versus 7.81%+-1.42%) and an eGFR that was clearly lower than the non-insulin group (82.81+-28.33 versus 92+-25.19 mL/min/1.73m^2). The average age did not vary between both groups. HbA1c and the lower eGFR of the insulin group confirmed poorer metabolic control and the association with a greater decrease in eGFR.[13] No differences were found in eGFR control in patients receiving metformin, DPP4i, or SGLT2i, from which it can be deduced that dulaglutide is effective in maintaining eGFR independently of other antidiabetic drugs. Furthermore, almost 80% of the patients took RAAS drugs as we have previously noted.

Conclusions Based on the 36M follow-up results, dulaglutide was shown to be an effective and nephroprotective drug in diabetic patients, allowing an metabolic control. These results are the first published real-life data obtained over an extended study period and allow us to confirm the beneficial results of dulaglutide in renal and metabolic functions.

Conflict of interest statement

All the authors who have contributed to this research declare that they have NO conflicts of interest.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables:

Table 1

	Total	Insulin	No insulin
Patients (n)	87	51	36
Age (years) (SD)	57.88 (9.96)	58.01 (8.98)	57.71 (11.34)
Male/Female (%)	39.07/60.93	39.22/60.78	38.89/61.11

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	Total	Insulin	No insulin
Creatinine (mg/dl) (SD)	0.83 (0.27)	0.89 (0.28)	0.79 (0.27)
eGFR ($mL/min/1.73m^2$) (SD)	88.10 (±26.47)	82.81 (±28.33)	92.72 (±25.19)
Initiating treatment, n (%)			
Metformin	72 (82.75)	39 (76.47)	33 (91.66)
Sulfonylureas	23 (26.43)	13 (25.49)	10 (27.77)
DPP-4i	31 (35.63)	20 (39.21)	11 (30.55)
SGLT2i	31 (35.63)	15 (29.41)	16 (44.44)
Insulin	51 (58.62)	51 (100)	36 (0)
ACEIs/ARBs	68 (78.16)	43 (84.31)	25 (69.44)
Diuretics	50 (57.47)	29 (56.86)	21 (58.33)
Antihyperglycemic drugs (without insulin), n (%)			
0	5 (5.74)	4 (7.84)	1 (2.77)
1	31 (35.63)	18 (35.29)	13 (36.11)
2	32 (36.78)	19 (37.25)	13 (36.11)
[?]3	19 (21.84)	10 (19.60)	9 (25)
Glucose (mg/dl) (SD)	174.22 (66.25)	175.91 (72.79)	162.89 (46.99)
HbA1c (%) (SD)	8.53 (1.91)	8.87 (1.97)	7.81 (1.42)
Weight (kg) (SD)	102.20 (19.64)	98.68 (14.38)	108.66 (26.02)

Table 1: Patient demographic and clinical characteristics at baseline (total and differences according insulin treatment). Values are expressed as mean ± standard deviation (SD). DPP-4 Inhibitors: dipeptidyl peptidase-4 inhibitors; SGLT2 Inhibitors: sodium glucose cotransporter 2 inhibitors. eGFR: estimated glomerular filtrate rate. ACEIs/ARBs: Angiotensin-converting-enzyme inhibitors/Angiotensin II receptor blockers.

Table 2

Analytical variable	**Time (months)**	**Time (months)**	**Time (months)**	**Time (mon**
	Basal	**12 M**	**24 M**	**36 M**
Creatinine (mean ± SD) (mg/dL)	0.83±0.27	0.87±0.26	0.84±0.26	0.90±0.36
eGFR (mean ± SD) ($ml/min/1.73m^2$)	88.10±26.47	82.40±24.35	85.21±24.47	83.25±29.27
eGFR patients with insulin ($ml/min/1.73m^2$)	82.81±28.33	76.34±25.34	81.73±25.74	77.42±29.84
eGFR patients without insulin ($ml/min/1.73m^2$)	92.72±25.19	91.28±24.01	89.41±22.52	89.36±28.14
Glucose (mean ± SD) (mg/dL)	174.22±66.25	139.20±45.63	144.90±47.58	151.51±59.0
HbA1c (mean ± SD) (%)	8.53±1.91	7.14±1.08	7.24±1.17	7.22±1.50
Weight (mean ± SD) (Kg)	102,20 (±19,64)	98,56 (±15,86)	98,39 (±16,46)	99,03 (±16,2

Table 2: Analytical variable evolution over 36 months (M). Creatinine and glomerular filtration rate (GFR) results according to the oral antidiabetic drug. Values are expressed as in mean ± standard deviation (SD). DPP-4i: dipeptidyl peptidase-4 inhibitors; SGLT2i: sodium glucose cotransporter 2 inhibitors.

Table 3

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Analytical variable	**Drug intake**	**Time (moths)**	**Time (moths)**	**Time (moths)**	**Time (moths)**	**Time (moths)**	**Time (moths)**	**Time (moths)**	**Ti (m**
	Metformin	**Basal**	**p-value**	**12M**	**p-value**	**24M**	**p-value**	**36M**	**p-va**
Creatinine (mean ± SD)	No	0.92±0,24	0.257	0.96±0.34	0.263	0.91±0.30	0.320	0.91±0.29	0.9
	Yes	0.83±0.29		0.86±0.29		0.83±0.25		0.90±0.37	
Glomerular filtrate (mean ± SD)	No	77.27±23.43	0.149	77.42±28.57	0.397	80.94±28.19	0.491	80.33±30.34	0.7
	Yes	88.84±27.81		83.68±25.17		85.79±23.92		82.28±29.59	
	Sulfonylureas								
Creatinine (mean ± SD)	No	0.84±0.26	0.700	0.89±0.31	0.454	0.85±0.28	0.607	0.91±0.36	0.8
	Yes	0.86±0.33		0.84±0.25		0.82±0.20		0.89±0.37	
Glomerular filtrate (mean ± SD)	No	88.32±27.59	0.450	82.36±25.80	0.901	85.51±25.21	0.729	82.71±30.08	0.8
	Yes	83.24±26.95		83.16±26.18		83.41±23.35		81.08±28.82	
	DPP-4i								
Creatinine (mean ± SD)	No	0.83±0.26	0.554	0.86±0.25	0.534	0.86±0.28	0.549	0.92±0.36	0.6
	Yes	0.87±0.31		0.90±0.36		0.82±0.22		0.88±0.36	
Glomerular filtrate (mean ± SD)	No	87.49±26.05	0.811	82.82±24.22	0.904	84.40±25.87	0.782	80.67±29.84	0.5
	Yes	86.01±29.94		82.11±28.70		85.94±24.60		85.12±29.40	
	SGLT2i								
Creatinine (mean ± SD)	No	0.85±0.29	0.747	0.90±0.32	0.321	0.84±0.27	0.800	0.89±0.34	0.7
	Yes	0.83±0.27		0.83±0.25		0.85±0.23		0.92±0.39	
Glomerular filtrate (mean ± SD)	No	87.02±29.96	0.980	80.51±24.20	0.329	87.05±25.34	0.292	83.31±29.60	0.6
	Yes	86.86±28.49		86.27±28.35		81.20±23.26		80.44±29.95	
	Insulin								
Creatinine (mean ± SD)	No	0.79±0.27	0.101	0.78±0.25	**0.013**	0.80±0.26	0.167	0.82±0.36	0.0
	Yes	0.89±0.28		0.95±0.31		0.88±0.25		0.96±0.35	

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Analytical variable	**Drug intake**	**Time (moths)**	**Time (moths)**	**Time (moths)**	**Time (moths)**	**Time (moths)**	**Time (moths)**	**Time (moths)**	**Ti (m**
Glomerular filtrate (mean ± SD)	No	92.72±25.19	0.098	91.28±24.01	**0.008**	89.41±22.52	0.155	89.36±28.14	0.0
	Yes	82.81±28.33		76.34±25.34		81.73±25.74		77.42±29.84	

Table 3: Parameters evolution through follow-up to 36M. eGFR: estimated glomerular filtration rate; HbA1c: glycosylated hemoglobin. Values expressed as in mean ± standard deviation (SD).

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