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Original Research

Combination Therapy With Glucagon-Like Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors in Older Patients With Type 2 Diabetes: A Real-World Evidence Study

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Key Messages

- The benefits of the combination of GLP1ra and SGLT2i have been shown in clinical trials and observational reports, but scientific literature concerning older patients is scarce.
- Our sample was significantly older and obese; even so, the results confirm the evidence of clinically meaningful reductions in glycated hemoglobin levels, body weight and systolic blood pressure.
- In our cohort, 46% of patients were taking insulin. Severe hypoglycemia was low, providing further evidence regarding security with the use of this combination in older patients.

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ABSTRACT

Objectives: Scientific literature about the combination of glucagon-like peptide-1 receptor agonists (GLP-1ra) and sodium-glucose cotransporter 2 (SGLT2) inhibitors in older patients is scarce. We sought to assess the real-world efficacy and safety of SGLT2 inhibitors and GLP-1ra combination therapy in older patients (>65 years of age).
Methods: This was an observational, prospective, multicenter study based on clinical practice. Patients were stratified according to tertiles of baseline glycated hemoglobin (A1C) levels and to treatment schedule.
Results: We included 113 patients (65.5% men, mean age 70.4±8.8 years). The body mass index was 36.5 (±6.6) kg/m^2. The baseline A1C level was 8.0% (±1.2%). At the 6-month follow up, we found a significant reduction in A1C levels (−1.1%; p<0.0001), body mass index (−2.1 kg/m^2; p<0.00003) and systolic blood pressure (−13 mmHg; p<0.000005). Patients who had the highest baseline A1C levels (≥8.4%) showed greater improvement in A1C levels (p<0.0001), weight (p<0.0001) and quality-of-life scores (p<0.0001). The greatest reduction in A1C levels and weight was seen in patients who started both drugs simultaneously (p<0.0001). The second greatest reduction was seen when GLP-1ra was added to previous treatment with an SGLT2i (p<0.0001). Also of note was a decrease in systolic blood pressure in patients for whom an SGLT2i was added to previous GLP-1ra treatment (p<0.0001). Of the patients, 34.3% achieved the combined endpoint of A1C levels <7% and weight loss ≥5% without hypoglycemia.
Conclusions: This study's findings provide evidence of clinically meaningful reductions in A1C level, body weight and systolic blood pressure in older patients with type 2 diabetes who are taking combined regimens. The dropout and hypoglycemia rates were minimal, and treatment was tolerated well.

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RÉSUMÉ

Objectifs : La littérature scientifique sur la combinaison des agonistes des récepteurs du GLP-1 et des inhibiteurs du SGLT2 chez les patients âgés est peu abondante. Nous avons cherché à évaluer l'efficacité et l'innocuité en contexte réel de la combinaison des inhibiteurs du SGLT2 et des agonistes des récepteurs GLP-1 chez les patients âgés (>65 ans).

Méthodes : Il s'agissait d'une étude observationnelle, prospective et multicentrique fondée sur la pratique clinique. Nous avons réparti les patients en fonction des tertiles des concentrations initiales de l'hémoglobine glyquée (A1c) et du schéma thérapeutique.

Résultats : Nous avons sélectionné 113 patients (65,5 % d'hommes, âge moyen de 70,4±8,8 ans). L'indice de masse corporelle était de 36,5 (±6,6) kg/m². La concentration initiale de l'A1C était de 8,0 % (±1,2 %). Au suivi après 6 mois, nous avons observé une réduction significative des concentrations de l'A1C (−1,1 %; p<0,0001), de l'indice de masse corporelle (−2,1 kg/m²; p<0,00003) et de la pression artérielle systolique (−13 mmHg; p<0,000005). Les patients qui avaient les concentrations initiales les plus élevées de l'A1C (≥8,4 %) montraient une plus grande amélioration des concentrations de l'A1c (p<0,0001), du poids (p<0,0001) et des scores de qualité de vie (p<0,0001). Une plus grande réduction des concentrations de l'A1C et du poids était observée chez les patients qui commençaient simultanément les deux médicaments (p<0,0001).

La deuxième plus grande réduction était observée lors de l'ajout des agonistes des récepteurs du GLP-1 au traitement par inhibiteur du SGLT2 (p<0,0001). On notait aussi une diminution de la pression artérielle systolique chez les patients auxquels on avait ajouté un inhibiteur du SGLT2 au traitement par agoniste des récepteurs du GLP-1 (p<0,0001). Parmi les patients, 34,3 % atteignaient le critère d'évaluation combiné (concentrations de l'A1c<7 % et perte de poids≥5 % sans hypoglycémie.

Conclusions : Les résultats de la présente étude montrent des preuves de réductions significatives des concentrations de l'A1c, du poids corporel et de la pression artérielle systolique chez les patients âgés atteints du diabète de type 2 qui suivent un schéma posologique combiné. Les taux d'abandon et d'hypoglycémie étaient minimes, et le traitement était bien toléré.

Mots clés :
du poids corporel
régulation de la glycémie
agonistes des récepteurs du GLP-1
patients âgés
inhibiteurs du cotransporteur sodium-glucose de type 2

Introduction

The global prevalence of diabetes is estimated to increase to 642 million by 2040, and the largest age-specific rise is predicted to be among people between 60 and 79 years of age. Currently, approximately 20% of people between 70 and 79 years of age are thought to have diabetes (1). Comprehensive treatment of type 2 diabetes requires the correction of hyperglycemia, body weight, blood pressure, insulin resistance and avoiding the risk for hypoglycemia, especially in older people (2,3). Results from the National Health and Nutrition Examination Survey (NHANES I and II) indicated that almost half of all patients did not meet the recommended glycated hemoglobin (A1C) level goal of <7.0% (4,5).

Two classes of drugs that have been developed recently, glucagon-like peptide-1 receptor agonists (GLP-1ra) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), have heralded a new era in the treatment of type 2 diabetes. Separately, both have been shown in clinical trials to have beneficial effects on glycemic control, body weight and cardiovascular risk factors (6–9). GLP-1ra act directly on the pancreas, gastrointestinal tract and brain. They also act indirectly on adipose tissue, muscle and the liver, increasing lipolysis and energy expenditure in adipose tissue and glucose uptake in muscle (10–12). SGLT2i act directly on the kidney, causing a glucose-dependent glucoretic effect that can result in the elimination of approximately 60 g to 100 g of glucose per day (13), with consequent weight loss (14). Glucosuria improves insulin sensitivity; it lowers plasma insulin levels and raises glucagon concentrations, which may be part of the SGLT2i-induced ketogenesis mechanism (the "thrifty substrate" theory) (15,16). Furthermore, glucose-dependent mechanisms minimize the risk for hypoglycemia.

The benefits of the combination of these 2 drugs have been shown in 3 randomized clinical trials (17–19) and in several short observational reports (20–24). However, scientific literature about the combination in older patients is scarce (25).

This study assesses the real-world efficacy and safety of this novel combination of SGLT2i and GLP-1ra therapy in older patients with type 2 diabetes who have suboptimal glycemic control.

Methods

This was an observational, prospective, multicenter study based on clinical practice. Its goal was to assess the efficacy and safety of the combined use of SGLT2i and GLP-1ra in outpatients attended to by the Internal Medicine Departments between October 2016 and April 2017.

Patients

Patients older than 65 years of age whose A1C levels were >7% and who received GLP-1ra and SGLT2i combination therapy were included. The inclusion criteria were being 65 to 80 years of age, having A1C levels between 7% and 10% and bing treated with GLP-1ra and SGLT2i in accordance with usual clinical practice. The exclusion criteria were type 1 diabetes mellitus, medical histories of diabetic ketoacidosis, complex insulin therapies (more than 2 daily doses), estimated glomerular filtration rates (eGFRs) of <45 mL/min/m² and medical histories of either medullary thyroid cancer or pancreatitis.

Patients were stratified into 3 tertiles according to baseline A1C levels: the first tertile had A1C levels ≤7.6%; the second tertile had A1C levels >7.6% to ≤8.4%; the third tertile had A1C levels >8.4%. Additionally, patients were analyzed in 3 groups according to the sequential order of treatment—i.e. the addition of a GLP-1ra before an SGLTi, an SGLT2i before a GLP1ra or both agents initiated simultaneously.

The data were collected in an anonymized electronic registry. This work was conducted in accordance with the ethical principles for research on human beings outlined in the Declaration of Helsinki and updated at the General Assembly of Brazil (2013). The confidentiality and secrecy of personal information were respected. The study was approved by the Clinical Research Ethics Committee of the University Hospital of Badajoz.

Assuming a decrease in A1C levels of 0.5% at 6 months (17–24), with an error of 2% and a confidence interval of 95%, the minimum sample size would be 60 patients. Calculating a percentage of losses of 10% at 6 months, the final sample required would be 66 patients.

Variables

Clinical and anthropometric variables were obtained from all participating paients. Their eGFRs were calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (26). The quality-of-life (QOL) score was measured using the EuroQol 5-dimension scale (27).

Hypoglycemia was defined as symptoms of hypoglycemia and plasma glucose levels <3.9 mmol/L. Severe hypoglycemia was defined as hypoglycemic episodes in which the patient needs the assistance of a third person or those in whom plasma glucose levels are <2.8 mmol/L.

Endpoints

The primary endpoint was to assess changes in A1C levels at 3 and 6 months in the entire cohort and in the prespecified groups (A1C levels and treatment schedules).

The secondary endpoints were the changes in body weight, systolic blood pressure (SBP) and diastolic blood pressure, lipid profile, eGFR and albuminuria as well as the percentage of patients who achieved A1C levels <7%, BMI <30 kg/m^2 and blood pressure <130/80 mmHg or A1C levels <7% and weight loss greater than 5% without hypoglycemia (28).

Statistical analysis

We used robust statistical methods that were not affected by outliers. Qualitative variables were expressed as absolute numbers (percentage). In order to compare these variables among subgroups, we used the chi-square test. Quantitative variables were expressed as 20% trimmed mean (median absolute deviation). In order to compare these variables among subgroups, we used the ANOVA function in the case of normal distribution and the Welch t test in the case of unequal variance. The Rust-Fligner test was used for the remaining variables. To compare the results during the follow-up period, we used the paired t test when normality and homoscedasticity were proven, and we used the paired Wilcoxon signed-rank test for the remaining variables. The differences were expressed as 20% trimmed mean, and the confidence interval was 95%. All statistical analyses were performed using R, v. 3.3.2. p<0.05 was considered statistically significant.

Results

We included 113 patients (65.5% men). The 20% trimmed mean of age was 70.4 (±8.8) years. Patients had had type 2 diabetes for a mean of 9.2 (±5.9) years. The mean BMI was 36.5 (±6.6) kg/m^2, and the waist diameter was 118.4 (±13.3) cms. Their baseline A1C and eGFR levels were 8.04 (±1.2)% and 87.5 (±20.9) mL/min/m^2, respectively.

Regarding comorbidities, 69.9% had histories of hypertension, 82.3% of dyslipidemia, 19.5% of coronary artery disease and 9.73% of heart failure.

The most commonly used GLP1ra were liraglutide (52.2%), then dulaglutide (29.2%), exenatide lar (8.84%), lixixenatide (5.31%) and albiglutide (4.42%). In the case of SGLT-2i, the most frequently used were canagliflozin (58.4%), then dapagliflozin (26.5%) and empagliflozin (15.04%). Of the patients, 52 (46%) were being treated with insulin at a mean baseline dosage of 39.4 (±19.5) units.

Follow up at 3 and 6 months

The principal findings of the follow up are shown in Table 1 and Figure 1. We found a significant reduction in fasting plasma glucose levels at the sixth month (2.2 mmol/L; p<0.0004); in A1C levels (1.14%; p<0.0001); in BMIs (2.1 kg/m^2; p<0.00003); and in systolic blood pressure (p<0.000005), among other factors. In this series, 64.8% of patients managed to reduce A1C levels to under 7%, 20% reduced BMIs to under 30 kg/m^2, and 66.6% reduced blood pressure to under 130/80 mmHg; 37 patients (34.3%) achieved the combined endpoint of A1C levels <7% and weight loss ≥5% without hypoglycemia.

Results by subgroup of A1C levels

Table 2 and Figure 1A show the findings according to the baseline A1C sugroup. Patients who had the highest baseline A1C levels saw greater decreases in A1C levels (p<0.0001), weight (p<0.0001) and QOL scores (27) (p<0.0001) at 6 months after beginning their treatment. At 6 months, the drop in SBP was similar in both the higher and the lower baseline A1C level groups (−7. 6 mmHg, 95% CI 3.8 to 11.5 mmHg; p<0.0001 and −7.7 mmHg, 95% CI 2 to 13.3 mmHg; p<0.05, respectively).

Table 1
Clinical and anthropometric variables at baseline, 3 and 6 months

Variable	Baseline	3 months	p	6 months	p
FPG (mg/dL)	9±2.6	7.4±2	0.0025	6.8±1.9	0.00046
A1C (%)	8.0±1.2	7.2±0.8	0.0003	6.9±0.9	0.0001
Total cholesterol (mg/dL)	165.4±42.9	163.9±38.5	0.89	163.1±34.8	0.47
LDL-C (mg/dL)	90±31.1	86.01±34.1	0.3	84.5±25.9	0.1
HDL-C (mg/dL)	41.3±8.9	41.8±11.9	0.44	43.8±11.1	0.02
Tg (mg/dL)	172.4±74.1	160.8±75.6	0.15	141.3±54.1	0.0003
Hematocrit (%)	41.4±4.4	42.2±4.4	0.003	42.6±5.2	0.006
Uric acid (mg/dL)	5.2±1.6	4.7±1.6	0.006	4.6±1.5	0.000007
eGFR (mL/min/1.73 m^2)	87.5±20.9	86.5±22.9	0.49	86.1±22.7	0.3
Sodium (mmol/L)	139.7±2.9	139.2±3.1	0.3	140±2.9	0.3
Potassium (mmol/L)	4.4±0.4	4.3±0.4	0.4	4.3±0.4	0.15
Weight (kg)	101.6±21.3	96.8±17.7	0.0004	95.5±19	0.000002
WC (cm)	118.4±13.3	113.4±13.3	0.000004	111.4±14.8	0.0000009
BMI (kg/m^2)	36.5±6.6	34.8±5.3	0.0008	34.4±5.7	0.00003
SBP (mmHg)	136.1±17	131.2±14.8	0.0001	129.1±14.8	0.00005
DBP (mmHg)	77.4±10.3	75.96±8.9	0.1	74.3±7.4	0.001
QOL	94.8±4.4	91.9±7.41	0.0000	89.3±11.8	0.0000
HR (bpm)	75.4±5.9	75.3±5.9	0.8	73.7±8.9	0.03
Insulin users (n)	52 (46%)			42 (38.8%)	0.0001
Insulin doses (U/day)	39.8±21.4			32.5±18.2	0.0008

A1C, glycated hemoglobin; *BMI*, body mass index; *DBP*, diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *FPG*, fasting plasma glucose; *HR*, heart rate; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *QOL*, quality of life; *SBP*, systolic blood pressure; *Tg*, triglycerides; *WC*, waist circumference.

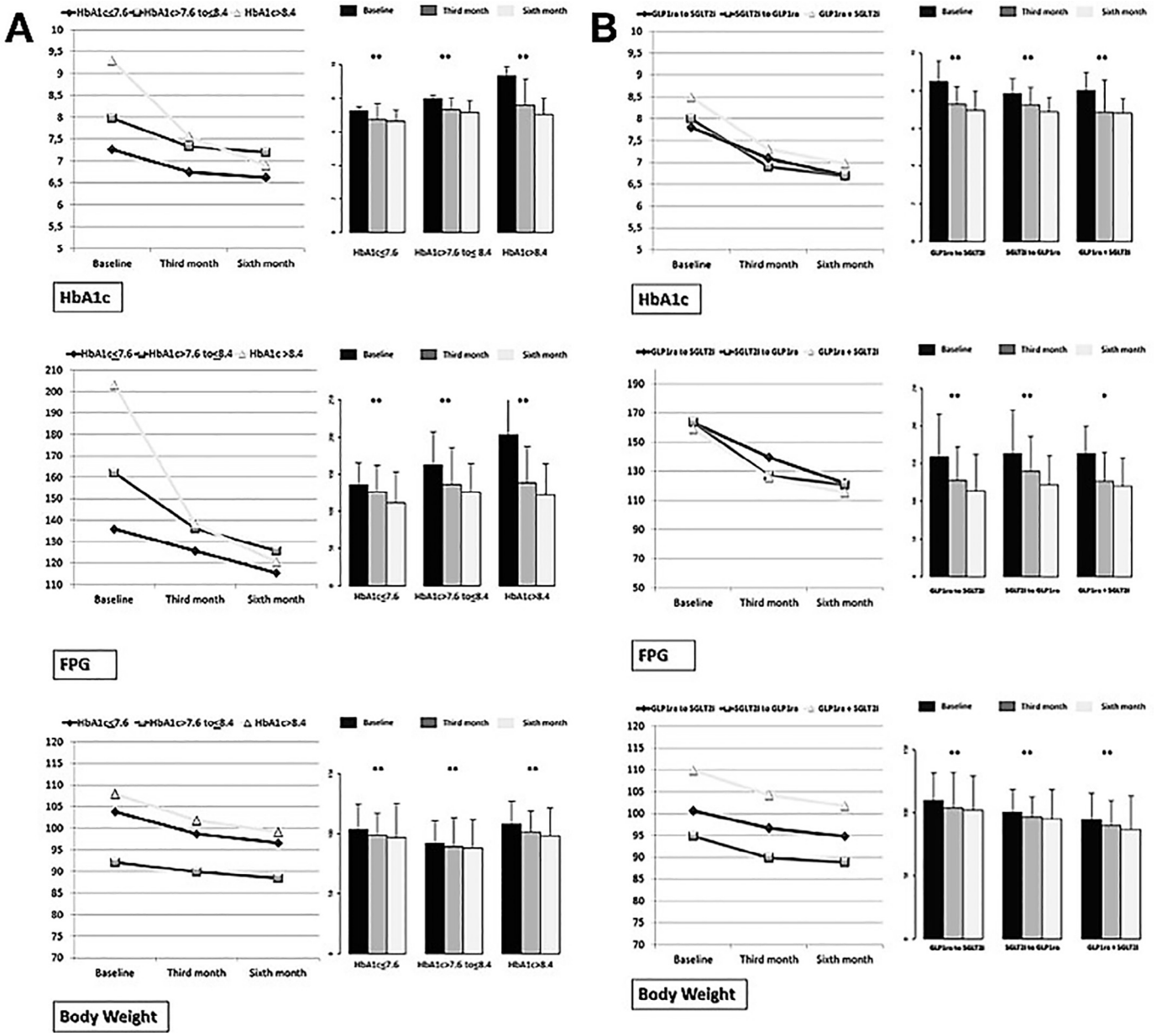

Figure 1. A, Changes in A1C, FPG and body weight from baseline to end of follow-up period according to predetermined A1C groups. B, Changes in A1C, FPG and body weight from baseline to end of follow-up period according to predetermined schedule groups (successively vs. simultaneously). *A1C*, glycated hemoglobin; *BMI*, body mass index; *FPG*, fasting plasma glucose; *GLP-1ra*, glucagon-like peptide-1 receptor agonists; *ND*, no date; *SGLT2i*, sodium-glucose cotransporter 2 inhibitors; *SBP*, systolic blood pressure. *p<0.05. **p<0.0001.

Results by treatment schedule subgroup

The sample was divided according to whether the patients began combined therapy with a GLP-1ra or an SGLT2i. In the first group, 59 patients (52.2%) were treated with a GLP-1ra for a mean of 12.6 (±4.9) months before an SGLT2i was added. In the second group, 24 patients (21.2%) started with an SGLT2i for 5.9 (±3.3) months before a GLP-1ra was added. Last, in the third group, 30 patients (26.5%) began a combination of both drugs simultaneously. Table 3 and Figure 1B show the principal findings. Regarding A1C levels, the greatest reduction at 6 months was seen in patients who started a combination of both drugs simultaneously (−1.5%, 95% CI 0.9 to2.1; p<0.0001). The second greatest reduction occurred in the group in which a GLP-1ra was added to previous treatment with an SGLT2i (−1.2%, 95% CI 0.6 to 1.8; p<0.0001). Concerning weight, a significant decrease (−7.6 kg, 95% CI 5.0 to 10.1; p<0.0001) was observed when the combination was started simultaneously. Also of note was a decrease in SBP in patients for whom an SGLT2i was added to previous GLP-1ra treatment (−8.2 mmHg, 95% CI 5.6 to 10.8; p<0.0001). Significant improvement in the QOL score was observed in all 3 subgroups.

Adverse events

During follow up, 1 patient died of a subarachnoid hemorrhage. Treatment with SGLT2i was discontinued in 4 patients (5.4%) at 3 months of follow up: 2 patients discontinued medication because of a genital mycotic infection, 1 because of worsening renal

Table 2
Predetermined baseline A1C groups

Predetermined groups	A1C ≤7.6%		A1C >7.6% to ≤8.4%		A1C >8.4%	
	Baseline	6 months	Baseline	6 months	Baseline	6 months
N	39	37	37	35	37	34
A1C						
20% tr mean (MAD)	7.3±0.15	6.6±0.5	7.8±0.1	7.2±0.6	9.3±0.7	6.9±1.1
Change (95% CI)		0.63 (0.4–0.8)†		0.8 (0.6–1.1)†		2.3 (1.9–2.7)†
Weight						
20% tr mean (MAD)	103.8±22.2	96.6±20.9	92.1±11.8	88.5±17.3	107.9±17.8	99.2±14.1
Change (95% CI)		7.16 (4.5–9.8)†		3.35 (1.56–5.14)†		8.7 (6.1–11.2)†
FPG						
20% tr mean (MAD)	7.5±1.1	6.4±1.9	9±2.1	7±1.8	11.3±2.6	6.7±2.0
Change (95% CI)		1.1 (0.5–1.7)†		2.0 (1.2–2.8)†		4.6 (3.3–5.8)†
SBP						
20% tr mean (MAD)	137.2±19.3	129.5±14.8	135.8±13.3	129.6±14.8	136.5±15.4	128.7±14.8
Change (95% CI)		7.6 (3.9–11.5)†		6.8 (2.3–10.1)*		7.7 (2–13.3)*
DBP						
20% tr mean (MAD)	76.1±8.9	72.8±5.9	76.4±8.8	73.9±7.4	76.6±7.4	71.7±5.9
Change (95% CI)		3.3 (0.1–6.4)*		2.1 (–0.9–5.1)		4.9 (1.4–8.3)*
QOL						
20% tr mean (MAD)	94.4±5.9	91.1±7.4	92±5.9	87.7±11.8	96.4±6.7	89.1±7.4
Change (95% CI)		4.9 (1.4–8.3)*		4.2 (1.2–7.2)*		7.3 (3.9–10.5)†

A1C, glycated hemoglobin; *DBP*, diastolic blood pressure; *FPG*, fasting plasma glucose; *SBP*, systolic blood pressure; *MAD*, median absolute deviation; *20% tr*, 20% trimmed mean.
* p<0.05.
† p<0.0001.

Table 3
Predetermined treatment schedule groups (successively vs. simultaneously)

Predetermined groups	SGLT2i added to GLP1ra		GLP1ra added to SGLT2i		GLP-1ra plus SGLT2i	
	Baseline	6 months	Baseline	6 months	Baseline	6 months
N	59	55	24	23	30	27
A1C						
20% tr mean (MAD)	7.8±0.8	6.7±0.7	8.0±0.8	6.7±1.0	8.5±1.5	7±1.2
Change (95% CI)		0.1 (0.7–1.2)†		1.2 (0.6–1.8)†		1.5 (0.9–2.1)†
Weight						
20% tr mean (MAD)	100.6±21.3	94.8±16.3	94.8±17.0	88.9±16.3	109.9±22.3	101.8±19.3
Change (95% CI)		5.7 (3.5–7.8)†		5.7 (1.7–9.8)†		7.6 (5.0–10.1)†
FPG						
20% tr mean (MAD)	9.1±2.9	6.8±1.6	9.1±1.4	6.7±1.8	8.8±3.1	6.4±1.9
Change (95% CI)		2.3 (1.5–3.1)†		2.4 (1.3–3.5)†		2.4 (0.9–3.9)†
SBP						
20% tr mean (MAD)	137.2±11.9	129.2±14.8	130±8.1	126.1±13.2	138.8±14.8	131.9±13.3
Change (95% CI)		8.2 (5.7–10.8)†		3.9 (–0.92.3–8.8)*		5.9 (1.2–10.5)*
DBP						
20% tr mean (MAD)	75.8±7.4	71.6±7.4	78.8±8.4	72.2±8.1	81.5±11.8	77.7±7.4
Change (95% CI)		4.2 (1.7–6.6)*		2.6 (–1.8–6.9)		3.8 (0.1–7.6)*
QOL						
20% tr mean (MAD)	94.0±4.4	89.0±10.3	91.9±7.5	83.1±9.7	96.7±4.4	93.1±6.7
Change (95% CI)		5.1 (2.8–7.5)*		8.9 (5.5–12.2)*		3.8 (1.0–6.5)†

A1C, glycated hemoglobin; *DBP*, diastolic blood pressure; *FPG*, fasting plasma glucose; *GLP-1ra*, glucagon-like peptide-1 receptor agonists; *MAD*, median absolute deviation; *20% tr*, 20% trimmed mean; *SBP*, systolic blood pressure; *SGLT2i*, sodium-glucose cotransporter 2 inhibitors.
* p<0.05.
† p<0.0001.

function, and 1 because of a leg amputation (under treatment with dapagliflozin). At 6 months, SGLT2i was discontinued in 4 other patients: 3 because of a genital mycotic infection and 1 because of bariatric surgery. The GLP-1ra was discontinued in 5 patients: 2 because of gastrointestinal effects, 2 because of insulin intensification and 1 because of worsening of renal function.

Regarding hypoglycemia, 6 patients (5.3%) presented with documented symtomatic hypoglycemia (<3.9 mmol/L) events, by either logbook or glucometer, at 3 months of follow-up, and another 3 (2.8%) presented at 6 months. No severe hypoglycemia was reported during follow up. All of these patients were receiving insulin therapy, and combined therapy with GLP-1ra and SGLT2i was not discontinued.

Discussion

In older patients with type 2 diabetes not previously well controlled, the use of the combination of GLP-1ra and SGLT2i therapy is more beneficial for glycemic control, weight and SBP than each of the drugs separately. Scientific literature concerning the combination of these 2 drugs in older patients with type 2 diabetes is scarce (25). Our results support what has been published to date in other studies about combined therapy (17–19). Frías and colleagues' DURATION 8 study (17) of combination exenatide LAR plus dapagliflozin, initiated simultaneously, found decreases in A1C levels, body weight and SBP at 28 weeks. Compared with this study, our study's subjects were significantly older and more obese and had

Table 4
Comparativeness across the various studies reported

	Age (yrs)	A1C baseline (%)	A1C last follow up (%)	Weight baseline (kg)	Weight last follow up (kg)	BMI baseline (kg/m^2)	BMI last follow up (kg/m^2)	SBP baseline (mmHg)	SBP last follow up (mmHg)
SGLT2i added to GLP1ra									
CANVAS study (18 weeks)	61	8.1	7.1	ND	ND	37.4	35.1	131.9	124.9
Deal et al (20 weeks)	57.4	8.8	7.7	107.2	104.13	ND	ND	134	132.8
Curtis et al (20 weeks)	54	10.6	7.7	113.3	110.7	ND	ND	ND	ND
Goncalves et al (28 weeks)	60.5	8.9	7.6	111	101	37.2	33.7	133	120
Carretero et al (28 weeks)	71.2	7.8	6.7	100.6	94.8	36.8	34.9	137.2	129.1
GLP1ras added to SGLT2i									
AWARD10 (24 weeks)	56.2	8	6.6	92.9	89.8	32.9	ND	129.7	125.2
Carretero et al (28 weeks)	70.4	8	6.7	94.8	88.9	34.6	32.8	130.8	126.1
GLP1ras plus SGLT2i									
Duration 8 (28 weeks)	54	9.3	7.3	91.9	88.3	ND	ND	130.5	126.5
Goncalves et al (28 weeks)	51	9.1	7.1	116	106	39.2	36	135	122
Carretero et al (28 weeks)	69.6	8.5	7	109.9	101.8	40.2	37.3	138.8	131.9

A1C, glycated hemoglobin; *BMI*, body mass index; *DBP*, diastolic blood pressure; *GLP-1ra*, glucagon-like peptide-1 receptor agonists; *SBP*, systolic blood pressure; *SGLT2i*, sodium-glucose cotransporter 2 inhibitors.

better-controlled type 2 diabetes despite having had the disease for longer, and 46% were receiving baseline insulin treatment. These differences could explain the differing results found in our study, given that both weight loss and the decrease in SBP were greater in our older population. As shown in Table 3 and Figure 1B, in 30 patients, both drug classes were started simultaneously. In a retrospective study of 46 patients treated sequentially (60.5±7.1 years of age) and 33 patients treated simultaneously (51±10 years of age), Goncalvez et al (24) observed reductions in A1C levels, body weight and SBP that were slightly greater than ours, again, with a difference in the ages of the populations.

High baseline A1C levels are independent predictors of greater reductions when using combination therapies (29,30). As shown in Table 2 and Figure 1A, the group in our study that had the highest A1C levels at baseline obtained greater benefits in terms of decreased A1C levels and weight and improvement in QOL without differences in SBP values. Interestingly, regarding changes in weight, patients with the lowest A1C levels at baseline had greater weight loss but smaller reductions in insulin dosage (−1.3 U/day) vs. the subgroup that had baseline A1C levels >7.6% to ≤8.4%, who had less weight loss and higher insulin dosage reductions (−12.2 U/day). This could be because intensification of the treatment was aimed more at weight reduction than glycemic control.

In a post hoc analysis of the CANVAS study (18) of 95 patients previously treated with a GLP-1ra, Fulcher et al, after intensifying canagliflozin dosages to 100 mg or 300 mg, obtained reductions in A1C and SBP values similar to those found in our study, except for the weight loss, which was greater. Again, our population was significantly older, and 46% had baseline insulin treatment.

To the best of our knowledge, there is only 1 clinical trial in which GLP1ra were added to the stable treatment with SGLT2i in patients with inadequately controlled type 2 diabetes. In the AWARD10 study (19), Ludvik et al, during 24 weeks, added dulaglutide to stable dosages of canagliflozin, dapagliflozin or empagliflozin. They found significant decreases in A1C levels and body weight. Compared with this study, our sample was significantly older and more obese, and 46% were receiving baseline insulin treatment (the AWARD10 patients were taking only metformin and SGLT2i before starting GLP1ra). Weight loss was greater in our older population.

Several other studies (20–24) have also shown improvements in A1C levels, body weight and blood pressure. The average patient age in all the aforementioned studies was around 57 years. Therefore, our data are the first to consider older patients with type 2 diabetes (70.4±8.8 years). In Table 4, we show the comparative findings of our study related to other research that has been reported.

Our data also show that simultaneous combination can lead to faster weight loss and A1C decreases than when they are started sequentially. Few studies have investigated the benefits of using multiple agents with complementary mechanisms of action, especially in older patients. The current clinical guidelines (2,25,31) advise that, in triple combinations, agents with complementary mechanisms of action should be used. In our results, both the dropout rate and hypoglycemia were minimal and showed good treatment tolerance. These findings could be useful, not only because of their clinical relevance but also to combat clinical inertia and improve overall adherence.

In terms of adverse effects, gastrointestinal side effects are not uncommon with the use of GLP-1ra (7). Bone fractures and a small increased risk for foot amputation have been reported for canagliflozin. Mycotic genital infections are seen in about 5% to 10% of patients (more often in women than in men) using SGLT2i (6,9). Euglycemic diabetic ketoacidosis has also been associated with use of these agents in rare cases, and it is commonly associated with insulin deficiency, acute illness and dehydration. It should be noted that, overall, our cohort tolerated both drugs (GLP1ra and SGLT2i) well. Additionally, it is known that insulin and sulfonylurea regimens carry high risks for hypoglycemia, especially in older people. In our cohort, 46% of patients were taking insulin, and the occurrence of severe hypoglycemia was fairly low (2.6%) at 6 months, providing further reassurance overall for the use of this combination in older patients.

This study has some limitations. First, as an observational study, it was subject to bias, and the lack of a comparative group did not allow for stronger conclusions. Second, the interpretation of the findings from our study is limited by the relatively small numbers of patients and by the relatively short duration of follow up. Third, we have not distinguished among differing dosages of the drugs because there were too few patients in the groups, despite the fact that we managed to include nearly double the necessary sample size.

Conclusions

In conclusion, use of the combination of GLP1ra and SGLT2i in older patients provides obvious clinical benefits, including reductions in A1C levels, weight and blood pressure. Use of either agent sequentially also provided similar benefits, and the combination appears to be both safe and effective, with low rates of reported adverse effects and hypoglycemic events in older patients. Our data provide real-world evidence and compliment the scarcely reported data to date in this group of patients.

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Author Disclosures

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Author Contributions

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