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Effect of exenatide twice daily and dapagliflozin, alone and in combination, on markers of kidney function in obese patients with type 2 diabetes: A prespecified secondary analysis of a randomized controlled clinical trial

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Abstract

Aims: To evaluate the effects of separate and combined use of the sodium-glucose cotransporter-2 (SGLT2) inhibitor dapagliflozin and the glucagon-like peptide-1 receptor agonist (GLP-1RA) exenatide on measures of kidney function.

Methods: In this prespecified secondary analysis of the DECREASE trial, we enrolled 66 obese patients with type 2 diabetes in a 16-week randomized double-blind placebo-controlled clinical trial to investigate the effects of dapagliflozin and exenatide twice daily, alone or in combination, versus placebo on 24-hour urinary albumin:creatinine ratio (UACR), creatinine and cystatin C-estimated glomerular filtration rate (GFR) and kidney injury molecule-1:creatinine ratio (KIM-1:Cr).

Results: At week 16, the mean UACR change from baseline was -39.6% (95% confidence interval [CI] -58.6, -11.9; $P = 0.001$) in the combined exenatide-dapagliflozin group, -18.1% (95% CI -43.1, 18.0; $P = 0.278$) in the dapagliflozin group, -15.6% (95% CI -41.4, 21.6; $P = 0.357$) in the exenatide group and -11.0% (95% CI -39.8, 31.5; $P = 0.552$) in the placebo group. Compared to placebo, UACR difference at week 16 in the exenatide-dapagliflozin group was -32.2% (95% CI -60.7, 16.9; $P = 0.159$). Effects were similar in 37 participants who were using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at baseline. Compared to placebo, in the exenatide-dapagliflozin group, an acute dip in estimated GFR was observed with creatinine-estimated GFR (-4.0 mL/min/1.73 m^2 [95% CI -9.3, 1.2]; $P = 0.129$) and cystatin C-estimated GFR (-10.4 mL/min/1.73 m^2 [95% CI -14.9, -5.8]; $P < 0.001$). The mean KIM-1:

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Cr difference in the combined treatment arm versus placebo was −43.8% (95% CI −73.5, 18.9; $P = 0.129$).

Conclusion: This prespecified secondary analysis suggests that combined therapy with exenatide and dapagliflozin may have synergistic effects on markers of kidney function compared to either therapy alone or placebo in obese patients with type 2 diabetes.

KEYWORDS

dapagliflozin, diabetic kidney disease, exenatide, GLP-1RA, glucagon-like peptide-1 receptor agonists, SGLT2 inhibitors

1 | INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon like peptide-1 receptor agonists (GLP-1RAs) are glucose-lowering drugs that improve glycaemic control, induce weight loss and decrease blood pressure in patients with type 2 diabetes. Moreover, SGLT2 inhibitors have been demonstrated in dedicated outcome trials to reduce the risk of kidney failure in patients with chronic kidney disease. Secondary analyses from cardiovascular outcome trials in patients with type 2 diabetes have shown that GLP-1RAs also slow progression of kidney function decline in patients with type 2 diabetes.[1,2]

Sodium-glucose cotransporter-2 inhibitors and GLP-1RAs reduce glycated haemoglobin (HbA1c) through distinct yet complimentary mechanisms of action. SGLT2 inhibitors block glucose reabsorption in the proximal tubule, resulting in increased urinary glucose excretion. GLP-1RAs stimulate the glucose-dependent release of insulin, decrease postprandial glucagon secretion, slow gastric emptying, and reduce food intake by inducing satiety. The benefits of SGLT2 inhibitor use on kidney outcomes are attributed to multiple effects including systemic and kidney-specific haemodynamic effects, enhanced erythropoiesis, and anti-inflammatory effects.[3] The mechanisms by which GLP-1RAs slow progressive kidney function decline are not completely understood, but may be secondary to improvements in glycaemic control, blood pressure and body weight, as well as anti-inflammatory and antioxidative effects.

Because of these different mechanisms, combination treatment with SGLT2 inhibitors and GLP-1RAs may have synergistic effects.[4–7] In patients with type 2 diabetes, concomitant use of SGLT2 inhibitors and GLP-1RAs has been shown to improve HbA1c control, enhance weight loss and decrease systolic blood pressure compared with monotherapy, without increased risk of hypoglycaemia.[8] However, there are still limited data on the effects of the combined use of SGLT2 inhibitors and GLP-1RAs on markers of kidney function. Therefore, we assessed in a randomized controlled trial the effects of exenatide, dapagliflozin, and their combination versus placebo on markers of kidney function in obese patients with type 2 diabetes.

2 | METHODS

2.1 | Study design

This was a prespecified secondary analysis of the DECREASE (Dapagliflozin Plus Exenatide on Central REgulation of Appetite in diabeteS typE 2) study: a 16-week, single-centre, randomized, double-blind, placebo-controlled trial, primarily designed to assess the separate and combined effects of dapagliflozin and exenatide on activity in central reward and satiety circuits in response to food-related stimuli. The study was approved by the Medical Ethics Committee of the University Medical Centre Amsterdam, the Netherlands (METc number 2017.307). The study was registered at clinicaltrials.gov (NCT03361098) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All participants provided informed consent before any study-specific procedure commenced.

2.2 | Study population

We recruited participants with type 2 diabetes, aged between 18 and 75 years with a body mass index between 27 and 40 kg/m^2. Participants were using stable doses of metformin and/or sulphonylurea derivatives for at least 3 months. HbA1c levels for participants treated with metformin monotherapy were 53 to 86 mmol/mol (7%-10%) and for metformin plus a sulphonylurea they were 58 to 86 mmol/mol (7.5%-10%). Exclusion criteria were an estimated glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2, a history of serious cardiovascular, renal or liver disease, malignancies (excluding basal cell carcinoma) and uncontrolled thyroid disease.

2.3 | Randomization and intervention

After baseline measurements, participants were randomly assigned using block randomization 1:1:1:1, performed by an independent trial pharmacist using computer-generated numbers, to: dapagliflozin 10 mg once daily and placebo exenatide twice daily; exenatide 10 μg twice daily and placebo dapagliflozin; dapagliflozin 10 mg once daily and

exenatide 10 μg twice daily; or placebo dapagliflozin and placebo exenatide. Exenatide (or matched placebo) was initiated at a dose of 5 μg twice daily, followed by a dose increase to 10 μg twice daily after 4 weeks, which was maintained until the end of the study. Participants were instructed to inject exenatide (or placebo) 15 to 30 minutes before breakfast and dinner subcutaneously and to take dapagliflozin (or matched placebo) at 8:00 PM during the 16-week treatment period. Adherence was followed up by counting the remaining capsules and injection pens. All study medications were provided by AstraZeneca. To maintain blinding of participants and investigators throughout the study, participants were treated with two injections and one tablet per day in a double-dummy design. There was no difference in appearance between exenatide and placebo injections or dapagliflozin or placebo capsules.

2.4 | Endpoints

Assessment of the separate and combined effects of dapagliflozin and exenatide on kidney variables was a prespecified secondary objective of the DECREASE study. The main study outcome for the present study was change from baseline to week 16 in urinary albumin:creatinine ratio (UACR), assessed in a 24-hour urine collection. Other endpoints were changes in estimated GFR (calculated with the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] serum creatinine equation[9] and the CKD-EPI cystatin C equation[10]), urinary kidney injury molecular-1 (KIM-1) to creatinine ratio (KIM-1:Cr), and systolic blood pressure.

2.5 | Procedures and measurements

After randomization, clinical visits occurred after 1.5, 8 and 16 weeks. Participants collected 24-hour urine samples at baseline and after 1.5 and 16 weeks' follow-up. Blood samples for assessment of clinical chemistry variables were also taken at these timepoints. Samples were analysed in the central laboratory of the UMC Amsterdam, including measurement of urinary albumin and creatinine, HbA1c, and serum creatinine. Cystatin C and urinary KIM-1 were measured by the central laboratory of the UMC Groningen on a multiplex platform (MesoScale Discovery). Systolic blood pressure, diastolic blood pressure and mean arterial pressure were measured using an automated oscillometric device (Dinamap; GE Healthcare, Little Chalfont, UK) in the brachial artery of the nondominant arm. Measurements were performed in triplicate at 2-minute intervals using the mean of the last two measurements.

2.6 | Statistical analysis

The study was designed to enrol 16 participants per treatment arm to assess the primary outcome of neuronal activity in central nervous system satiety and reward circuits, measured by blood oxygen level-dependent functional magnetic resonance imaging (MRI). For this secondary prespecified analysis, a sample size of 16 participants per treatment arm provided 50% power for the outcome of combined

exenatide-dapagliflozin versus placebo, assuming a 35% difference and geometric mean coefficient of variation in UACR of 66%.

The effect on UACR was estimated using a mixed-effects model repeated measures analysis, with log-transformed UACR change as a dependent variable. The model included the fixed effects of treatment assignment, visit and treatment-by-visit interaction, with covariates of baseline measurement and baseline-by-visit interaction. The contrasts between each active treatment group and the placebo group at week 16 were compared using a two-sided significance level of 0.05. The within-group geometric mean change (%) was derived by (1-exp(LS mean change)* − 100, and the same transformation was applied on the 95% confidence interval (CI) limits to obtain the 95% CI for the geometric mean change. GFR change was estimated using the same mixed-model repeated measures analysis. Estimated GFR was calculated using the CKD-EPI creatinine equation[9] and the CKD-EPI cystatin C equation.[10] The same model was also used to estimate changes from baseline and between-group differences in KIM-1:Cr, systolic blood pressure, body weight, and HbA1c. All analyses were performed in SAS version 9.4.

3 | RESULTS

3.1 | Baseline characteristics

Between December 2017 and January 2020, 106 people were screened, of whom 68 were included. Four participants were excluded during baseline testing because of previous unknown claustrophobia regarding the MRI scanner, before distribution of the study drugs. These four participants were replaced. Two participants dropped out just before the last test visit, one for personal reasons, the other because of ongoing nausea. The baseline demographics and clinical characteristics of the trial participants are shown in Table 1. The mean age was 64 years and the mean estimated GFR was 86 mL/min/1.73 m^2. The median UACR levels were in the high normal range. Overall, 22 participants (33.3%) had micro- or macroalbuminuria. Approximately half of recruited participants used an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). For all participants, the medications used at baseline, including ACE inhibitors and ARBs, remained unchanged during the study. All baseline characteristics were generally well balanced among treatment groups.

3.2 | Effects on kidney function variables

At baseline, the geometric mean UACR was 1.6 mg/mmol (95% CI 0.5 to3.0). After 16 weeks of treatment, UACR change was −11.0% (95% CI −39.8 to 31.5; P = 0.552) in the placebo group, −15.6% (95% CI −41.4 to 21.6; P = 0.357) in the exenatide group, −18.1% (95% CI −43.1 to 18.0; P = 0.278) in the dapagliflozin group, and − 39.6% (95% CI −58.6% to −11.9%; P = 0.01) in the combined exenatide and dapagliflozin group. Accordingly, the between-group difference between placebo and exenatide-dapagliflozin in 24-hour UACR was −32.2% (95% CI −60.7 to 16.9; P = 0.159 [Figure 1A]). Effects were

TABLE 1 Baseline characteristics of DECREASE participants

	Placebo (n = 17)	Exenatide (n = 17)	Dapagliflozin (n = 16)	Combination (n = 16)	Total (66)
Age, years	61.5 (7.2)	65.0 (5.8)	64.1 (8,4)	63.9 (7.4)	63.6 (7.2)
Sex: male	13 (76.5)	11 (64.7)	12 (75.0)	12 (75.0)	48 (72.7)
Diabetes duration, years	10.4 (7.5) 9.5 [7, 10.5]	10.0 [6, 18]	8.0 [5.5, 13.5]	7 [5, 12.8]	8.5 [6, 12.5]
Body mass index, kg/m^2	31.5 (5.7)	32.7 (5.1)	31.7 (3.3)	30.9 (3.4)	31.7 (4.5)
Systolic BP, mmHg	133.3 (13.1)	132.1 (11.1)	136.4 (10.7)	130.3 (10.8)	133.0 (11.4)
Diastolic BP, mmHg	81.3 (6.6)	81.0 (7.2)	80.8 (5.8)	79.7 (6.8)	80.7 (6.5)
HbA1c, mmol/mol	64.7 (11.5)	65.0 (11.1)	61.3 (6.0)	63.5 (14.5)	63.7 (11.0)
eGFR$_{creatinine}$, mL/min/1.73 m^2	86.2 (10.0)	83.6 (14.7)	85.1 (16.5)	90.4 (11.8)	86.3 (13.4)
eGFR$_{cystatin C}$, mL/min/1.73 m^2	79.4 (19.6)	78.8 (19.8)	79.3 (23.1)	84.7 (13.6)	80.5 (19.1)
UACR, mg/mmol	0.7 [0.5, 3.1]	1.0 [0.3, 2.4]	1.3 [0.5, 2.7]	1.9 [1.2, 3.5]	1.5 [0.5, 3.0]
Normoalbuminuria (<30 mg/24 h)	12 (70.6)	12 (70.6)	11 (68.8)	9 (56.3)	44 (66.7)
Micro-/macroalbuminuria (>30 mg/24 h)	5 (29.4)	5 (29.4)	5 (31.2)	7 (43.8)	22 (33.3)
Urinary KIM-1:Cr	46.1 [33.3, 60.7]	51.7 [26.3, 64.1]	49.1 [23.4, 60.9]	55.4 [32.2, 78.2]	50.2 [28.9, 63.1]
Concomitant medication					
ACE inhibitors or ARBs	10 (58.8)	12 (70.6)	5 (31.3)	10 (66.7)	37 (56.9)
Metformin	17 (100.0)	17 (100.0)	15 (93.8)	16 (100.0)	65 (98.5)
Sulphonylurea derivatives	9 (52.9)	6 (35.3)	5 (31.3)	3 (18.8)	23 (34.8)

Note: Data are given as mean (standard error) or median [interquartile range] for continuous metrics, and number (%) for categorical characteristics.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; KIM-1:Cr, kidney injury molecule-1:creatinine ratio; UACR, urinary albumin:creatinine ratio.

comparable when albuminuria was expressed as 24-hour urinary albumin excretion rate (Figure 1B). In the subgroup of 37 participants who were using an ACE inhibitor or ARB, the effect of combined exenatide-dapagliflozin compared to placebo on UACR was similar compared to the overall population (UACR difference − 43.2% [95% CI −75.4 to 31.1]; P value vs. placebo 0.177 [Figure 1C]).

After 16 weeks, a modest increase in urinary KIM-1:Cr was observed in the placebo group. In all active treatment groups KIM-1: Cr decreased, with the numerically largest decrease in the dapagliflozin group (Figure 1D). Change from baseline in KIM-1:Cr compared to placebo was −43.8% (95% CI −73.5 to 18.9; P = 0.129) in the exenatide-dapagliflozin group.
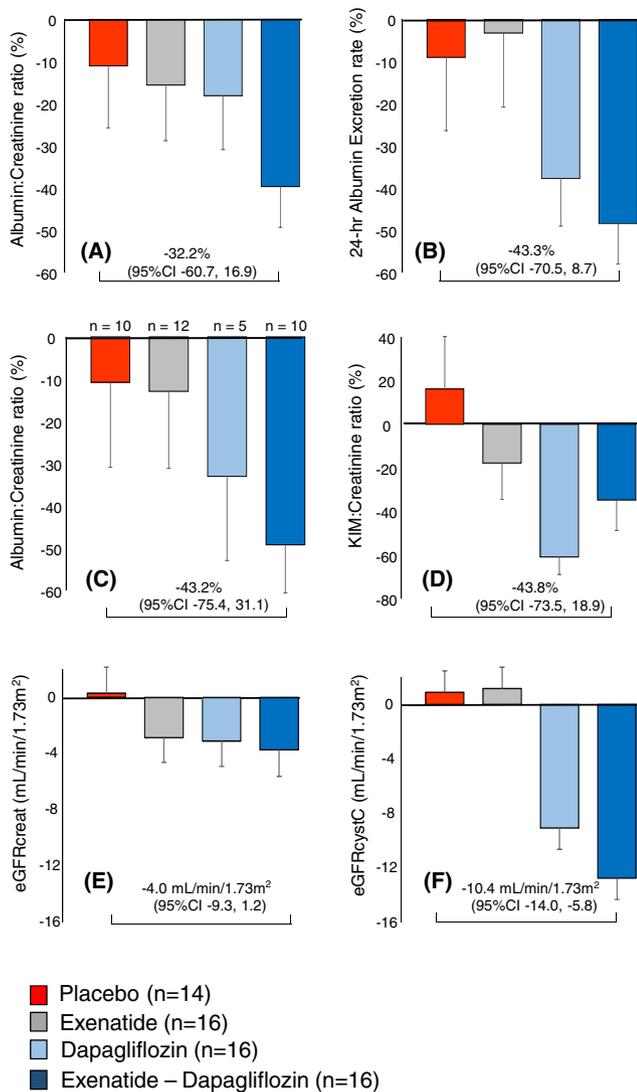
After 16 weeks of treatment, the mean creatinine-estimated GFR remained stable in the placebo group (0.3 mL/min/1.73 m^2 [95% CI −3.4 to 4.0]). An acute dip in creatinine-estimated GFR was observed in all active treatment groups (Figure 1C). Compared to placebo, change from baseline in creatinine-estimated GFR was −4.0 mL/min/1.73 m^2 (95% CI −9.3, 1.2; P = 0.129) in the exenatide-dapagliflozin combination group. In contrast to creatinine-estimated GFR, no change in estimated GFR was observed when GFR was estimated with cystatin C (Figure 1E,F). In the dapagliflozin and exenatide-dapagliflozin groups the reduction in cystatin C-estimated GFR was however substantially larger compared to creatinine-estimated GFR (Figure 1E,F). The difference between the placebo and exenatide-dapagliflozin group in cystatin C-estimated GFR was −10.4 mL/min/1.73 m^2 (95% CI −14.9, −5.8; P < 0.001 [Figure 1F]).

3.3 | Effects on metabolic risk factors

Treatment with placebo resulted in an HbA1c change of −3.4 mmol/mol (95% CI −7.0 to 0.1), which was statistically significantly smaller compared to the change with exenatide (−11.9 mmol/mol [95% CI −15.2 to −8.5; P vs. placebo <0.001), dapagliflozin (−8.6 mmol/mol [95% CI −12.1 to −5.2]; P vs. placebo <0.001) or exenatide-dapagliflozin (−15.5 mmol/mol [95% CI −19.0 to −12.0]; P vs. placebo <0.001). Combined exenatide-dapagliflozin led to a 6.1-mmHg (95% CI −12.6 to 0.4) reduction in systolic blood pressure compared to placebo (P = 0.065). Finally, the combination also reduced body weight more than single treatment or placebo. The corresponding body weight changes were −0.4 kg (95% CI −1.4 to 0.7) in the placebo group, −1.7 kg (95% CI −2.7 to −0.7; P = 0.067 vs. placebo) in the exenatide group, −2.8 (95% CI −3.9 to −1.8; P = 0.001 vs. placebo) in the dapagliflozin group, and −3.0 (95% CI −4.1 to −1.9; P < 0.001 vs. placebo) in the combined exenatide-dapagliflozin group.

3.4 | Safety

All treatments were generally well tolerated, there were slightly more adverse events in the combination group (P = 0.109). None of the participants had a hypoglycaemic event. There were no serious adverse events.

FIGURE 1 Changes in kidney function variables after 16 weeks' treatment with placebo (red, n = 14), exenatide (grey, n = 16), dapagliflozin (light blue, n = 16) and exenatide-dapagliflozin (dark blue, n = 16). A, Change in urinary albumin:creatinine ratio (UACR; %). B, Change in 24-hour urinary albumin excretion (%). C, Change in UACR in 37 participants (placebo, n = 10; exenatide, n = 12; dapagliflozin, n = 5; exenatide-dapagfliflozin, n = 10), using an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. D, Change in urinary kidney injury molecule-1:creatinine ratio (%). E, Change in creatinine-estimated glomerular filtration rate (eGFRcreat; mL/min/1.73 m^2). F, Change in cystatin C-estimated GFR (eGFRcystC; mL/min/1.73 m^2). CI, confidence interval; KIM, kidney injury molecule-1

4 | DISCUSSION

This secondary prespecified analysis of a randomized double-blind placebo-controlled trial assessed the effects of exenatide, dapagliflozin and their combination on kidney function variables in obese participants with type 2 diabetes. The combination of exenatide and dapagliflozin resulted in a larger reduction in albuminuria, estimated GFR, KIM-1, and metabolic risk factors compared to either

therapy alone or placebo. We note that not all comparisons reached statistical significance due to limited statistical power and should therefore be considered hypothesis-generating. A dedicated clinical trial is required to confirm these findings.

Glucagon-like peptide-1 receptor agonists have been shown to reduce albuminuria and slow progression of kidney function decline, particularly in patients with chronic kidney disease. For example, the AWARD-7 trial demonstrated that 12 months' treatment with dulaglutide compared to insulin reduced the rate of estimated GFR decline and albuminuria through an array of possible mechanisms including improved glycaemic and blood pressure control, augmented endothelial function, and anti-inflammatory effects.[11] The albuminuria-lowering effects of dulaglutide and other GLP-1RAs were mainly observed among participants with micro- or macroalbuminuria. As in the AWARD-7 trial, in the ELIXA trial, lixisenatide reduced albuminuria in patients with significant albuminuria at study entry: the observed reductions were 2% in patients with normoalbuminuria and 39% in patients with macroalbuminuria.[12] This may explain why in the present study, in which the majority of participants had normoalbuminuria, the albuminuria-lowering effect of exenatide was modest. SGLT2 inhibitors also reduce the risks of kidney failure in patients with type 2 diabetes, probably through reduction of intraglomerular pressure and glomerular hyperfiltration. The reduction in albuminuria with dapagliflozin compared to placebo was less than that observed in other studies.[13,14] Other studies enrolled patients with higher degrees of albuminuria where the effects of SGLT2 inhibitors have been more pronounced. The albuminuria-lowering effects of SGLT2 inhibitors are also smaller in patients with normoalbuminuria.[15,16]

Since GLP-1RAs and SGLT2 inhibitors confer kidney protection probably through different mechanisms of action, combining the two drug classes is a logical next step to augment kidney protection. Previous randomized controlled trials assessed the metabolic effects of combination treatment but none of these trials assessed the effect of GLP-1RAs and SGLT2 inhibitors on markers of kidney function. The results of the present study suggest that combination treatment reduces albuminuria to a substantially larger extent than placebo or single treatment with either therapy despite the fact that many participants were characterized by normoalbuminuria where the effects of the single agents have been modest.

A similar pattern was observed in a subgroup analysis of participants who were using renin-angiotensin system blockers, the current mainstay of kidney protective treatment. We note however that the CIs for the between-group differences were wide and the study was not powered to assess superiority of combination exenatide-dapagliflozin treatment versus monotherapy with these agents. However, the trend for enhanced effects is supported by an observational analysis from the EXSCEL randomized controlled trial which compared the effects of combined SGLT2 inhibition and exenatide versus exenatide and placebo treatment. After participants were propensity-score-matched, annual estimated GFR loss was significantly less in the combined treatment group compared to exenatide/placebo.[17] These findings are reassuring and collectively support the conduct of larger clinical trials to assess the effects on rate of estimated GFR decline

and clinically meaningful kidney endpoints of combined GLP-1RAs and SGLT2 inhibitor treatment.

Creatinine-based estimated GFR decreased in all active treatment groups. When GFR was estimated from cystatin C, the estimated GFR decrease was more pronounced in the dapagliflozin monotherapy group and the combination therapy group. However, in the exenatide group, change in cystatin C-estimated GFR was similar compared to placebo. Early reductions in estimated GFR following initiation of SGLT2 inhibitors have been observed in previous studies with SGLT2 inhibitors.[18,19] This reduction in estimated GFR does not represent glomerular function loss, but is a haemodynamic effect that reflects the mechanism of action and is supposedly associated with improved renal outcomes. Importantly, this initial "dip" in estimated GFR is reversible, with estimated GFR values returning to baseline within weeks after discontinuation of therapy. The difference in dip in estimated GFR based on serum creatinine and cystatin C is of interest and has been observed in a previous study as well.[20] Further study is warranted to explain these differences. It is possible that differences in non-GFR-based determinants which affect both creatinine (diet, muscle mass) and cystatin C levels (inflammation, obesity) are involved.[21]

During early development of both GLP-1RAs and SGLT2 inhibitors, concerns were expressed that both drug classes could increase the risk of acute kidney injury (AKI).[22,23] We therefore measured KIM-1, which is a marker of proximal tubular dysfunction and is increased in the setting of AKI. In the present analysis, we did not observe an increase in KIM-1 in any of the active treatment groups. In fact, KIM-1 values were lower after 16 weeks in these groups, with the decrease reaching statistical significance in participants who were treated with dapagliflozin. These findings support an increasing body of evidence demonstrating that GLP-1RAs do not cause AKI and SGLT2 inhibitors may even exert protective effects against AKI.[24]

Prior studies have assessed the effects of combination treatment with GLP-1RAs and SGLT2 inhibitors on metabolic risk factors. The DURATION-8 trial evaluated the combination of exenatide and dapagliflozin in patients with type 2 diabetes inadequately controlled on metformin. After 52 weeks, HbA1c reduction was greater with combination therapy versus exenatide and dapagliflozin monotherapy (−1.75% vs. −1.38% and −1.23%, respectively). In addition, combined treatment with exenatide and dapagliflozin resulted in nearly additive effects on weight loss and improvement in systolic blood pressure. In another trial in obese adults without diabetes, dual therapy with exenatide and dapagliflozin reduced body weight and SBP compared to placebo, and was well tolerated with no increase in hypoglycaemic episodes.[25] Two other trials evaluated the addition of GLP-1RAs (dulaglutide and semaglutide) to ongoing treatment with SGLT2 inhibitors in participants with type 2 diabetes. In both trials, the combination of both agents resulted in a larger reduction in HbA1c, body weight and systolic blood pressure compared to monotherapy with these agents.[6,7] The results of the DECREASE study confirm and extend these findings to obese adults with type 2 diabetes.

The present study has some limitations. Because the study was a prespecified secondary analysis it was not powered to assess the separate and combined effects of dapagliflozin and exenatide compared to placebo. As a result, some of the between-group comparisons did not reach statistical significance. We also did not adjust for multiple comparisons. For these reasons our results should be interpreted as hypothesis-generating. However, the markedly larger nominal reductions of exenatide-dapagliflozin compared to placebo on both 24-hour albuminuria excretion and UACR and the similarity of the effects in those with and without concomitant renin-angiotensin system blockade support a real effect, and future studies such as the ongoing DECADE trial (NTR 6839) will provide more information on the combined effects of SGLT2 inhibitors and GLP-1RAs. We also recognize that the majority of patients who were included in the DECREASE study had low levels of albuminuria and in such patients the absolute reductions in albuminuria are modest. As observed in other trials, dapagliflozin and exenatide-dapagliflozin caused a dip in estimated GFR.[13,26] This dip reflects favourable haemodynamic changes in the glomeruli and is reversible soon after treatment cessation.[3] We did not measure estimated GFR after treatment discontinuation and are therefore unable to assess whether the dip in estimated GFR is reversible in our study. In addition, the study population consisted of obese patients with type 2 diabetes, with a preserved estimated GFR (mean estimated GFR 80 mL/min). Therefore, our findings are limited to this specific population and cannot be generalized to other populations.

In conclusion, in obese patients with type 2 diabetes, combined therapy with exenatide and dapagliflozin may have additive effects on albuminuria, estimated GFR and metabolic risk factors compared to either therapy alone or placebo. These data support dedicated clinical trials to confirm the efficacy and safety of GLP-1RA/SGLT2 inhibitor combination treatment in improving kidney outcomes.

CONFLICT OF INTEREST

C.C.v.R. and A.B.v.d.A.v.d.B. have nothing to disclose. R.G.I.J. is principal investigator of studies sponsored by research grants from AstraZeneca, Eli Lilly & Co., and Novo Nordisk. M.N. serves on the Scientific Advisory Board of Caelus Pharmaceuticals, the Netherlands, and Kaleido, United States. R.G.I. and M.N. have reported that they received no personal payments in connection with the above-mentioned activities, but all payments were directly transferred to the nonprofit Amsterdam UMC. No other potential conflicts of interest relevant to this article were reported. K.H. has consulting relationships with Novo Nordisk and Sanofi, and receives research operating funding from Novo Nordisk. D.H.v.R. has consulting relationships with Boehringer Ingelheim, Eli Lilly, Merck and Sanofi, and receives research operating funding from AstraZeneca, Boehringer Ingelheim-Eli Lilly Diabetes Alliance and MSD. H.J.L.H. has consulting relationships with AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, CSL Pharma, Chinook, Dimerix, Gilead, Janssen, Merck, Mitsubishi Tanabe, Mundi Pharma, NovoNordisk, and Travere.

AUTHOR CONTRIBUTIONS

Charlotte C. van Ruiten and Richard G. IJzerman designed the DECREASE study. Charlotte C. van Ruiten conducted the study. Annemarie B van der Aart-van der Beek and Hiddo J. L. Heerspink wrote the first draft of the manuscript. Charlotte C. van Ruiten, Richard G. IJzerman, Max Nieuwdorp, Klaas Hoogenberg and Daniel H van Raalte participated in the interpretation of the data and revised the manuscript critically for important intellectual content. Hiddo J. L. Heerspink performed statistical analyses. All authors gave final approval to submit the article for publication.

PEER REVIEW

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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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