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Published in:
Diabetes, Obesity and Metabolism

DOI:
10.1111/dom.15033

Received: 18 January 2023 | Revised: 12 February 2023 | Accepted: 24 February 2023

DOI: 10.1111/dom.15033

WILEY

ORIGINAL ARTICLE

Albuminuria-lowering effect of dapagliflozin, exenatide, and their combination in patients with type 2 diabetes: A randomized cross-over clinical study

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Abstract

Aim: To evaluate the albuminuria-lowering effect of dapagliflozin, exenatide, and the combination of dapagliflozin and exenatide in patients with type 2 diabetes and microalbuminuria or macroalbuminuria.

Methods: Participants with type 2 diabetes, an estimated glomerular filtration rate (eGFR) of more than 30 ml/min/1.73m^2 and an urinary albumin: creatinine ratio (UACR) of more than 3.5 mg/mmol and 100 mg/mmol or less completed three 6-week treatment periods, during which dapagliflozin 10 mg/d, exenatide 2 mg/wk and both drugs combined were given in random order. The primary outcome was the percentage change in UACR. Secondary outcomes included blood pressure, HbA1c, body weight, extracellular volume, fractional lithium excretion and renal haemodynamic variables as determined by magnetic resonance imaging.

Results: We enrolled 20 patients, who completed 53 treatment periods in total. Mean percentage change in UACR from baseline was −21.9% (95% CI: −34.8% to −6.4%) during dapagliflozin versus −7.7% (95% CI: −23.5% to 11.2%) during exenatide and −26.0% (95% CI: −38.4% to −11.0%) during dapagliflozin-exenatide treatment. No correlation was observed in albuminuria responses between the different treatments. Numerically greater reductions in systolic blood pressure, body weight and eGFR were observed during dapagliflozin-exenatide treatment compared with dapagliflozin or exenatide alone. Renal blood flow and effective renal plasma flow (ERPF) did not significantly change with either treatment regimen. However, all but four and two patients in the dapagliflozin and dapagliflozin-exenatide groups, respectively, showed reductions in ERPF. The filtration fraction did not change during treatment with dapagliflozin or exenatide, and decreased during dapagliflozin-exenatide treatment (−1.6% [95% CI: −3.2% to −0.01%]; $P = .048$).

Conclusions: In participants with type 2 diabetes and albuminuria, treatment with dapagliflozin, exenatide and dapagliflozin-exenatide reduced albuminuria, with a numerically larger reduction in the combined dapagliflozin-exenatide treatment group.

KEYWORDS
albuminuria, chronic kidney disease, dapagliflozin, exenatide, SGLT2

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors have beneficial effects on multiple cardiovascular risk factors including albuminuria, and have been shown to reduce renal and cardiovascular risk in patients with type 2 diabetes and chronic kidney disease (CKD).[1,2] However, despite the availability of these new treatment options, a substantial proportion of patients still experience progressive kidney function decline, which is associated with persistently high levels of urinary albumin: creatinine ratio (UACR).[3-5] Novel treatment strategies to reduce this residual risk are therefore needed.

SGLT2 inhibitors and GLP-1 RAs slow the progression of CKD through apparently different mechanisms of action. SGLT2 inhibitors reduce intraglomerular pressure, improve tubular oxygenation and possibly induce changes in renal metabolism and fuel utilization.[6] Experimental and clinical studies reported that GLP-1 RAs mitigate inflammation and reduce oxidative stress, in addition to improving renal risk factors such as glycaemic control, body weight (BW) and hypertension.[7] Whether the combination of SGLT2 inhibitors and GLP-1 RAs more effectively reduces albuminuria and reduces glomerular filtration rate (GFR) decline compared with either drug alone has not been investigated in a prospective study, but could be expected given their different mechanisms of action and their additive effects on risk markers of CKD progression, as shown in prior studies.[8-11]

We designed the Dapagliflozin, Exenatide and Combination for Albuminuria reduction in Diabetes (DECADE) study to evaluate the albuminuria-lowering effect of dapagliflozin, exenatide, and the combination of dapagliflozin and exenatide in patients with type 2 diabetes and microalbuminuria or macroalbuminuria, and to further investigate possible mechanisms of action.

2 | METHODS

2.1 | Study design and patient population

The DECADE study was a randomized, prospective, open-label, single-centre, crossover clinical trial conducted in the Netherlands. The study included participants aged 18 years or older with type 2 diabetes, an estimated GFR (eGFR) of more than 30 ml/min/1.73m^2 and a UACR of more than 3.5 mg/mmol and 100 mg/mmol or less (> 30.9 and ≤ 884 mg/g). All participants were using stable doses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for at least 4 weeks before randomization. Key exclusion criteria included cardiovascular disease (myocardial infarction, angina pectoris, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, heart failure) for less than 6 months before inclusion, uncontrolled blood pressure (BP) (systolic/diastolic BP > 160/100 mmHg), rapid progression of kidney function decline (eGFR change > 30% in the 6 months before inclusion) and use of an SGLT2 inhibitor, GLP-1 RA or dipeptidyl peptidase 4 inhibitor for less than 6 weeks prior to screening. The study protocol was approved by the Regional Ethics Committee and registered at the International Clinical Trial Registry Platform (ICTRP) (EUCTR2017-004709-42-NL). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided their written informed consent before any study-specific procedure commenced.

2.2 | Study procedures

Participants were assigned a regimen consisting of three treatment periods, in which dapagliflozin 10 mg/d, exenatide 2 mg/wk and a combination of both drugs were given in random order. Each treatment period lasted 6 weeks, with washout periods of 9 weeks in between. The rationale for a 9-week washout period was based on pharmacokinetic analyses showing that after 9 weeks exenatide is no longer present in blood [Data on file AstraZeneca]. During the washout periods no changes were made in concomitant antidiabetic treatments in order to properly assess off-drug effects. Study visits were scheduled at the start, midway and end of each treatment period. At the start and end of each treatment period, participants collected three consecutive first morning void urine samples for urinary biochemistry assessments. The evening before the first and last treatment visit of each treatment period, participants took a 300-mg lithium tablet to allow for calculation of fractional lithium excretion, a proxy for sodium reabsorption in the proximal tubule.[12]

2.3 | Measurements

2.3.1 | Physical and biochemistry measurements

BW, heart rate and systolic/diastolic BP were measured at each study visit. BP was measured in sitting position after a 5-minute rest; the

mean of the three readings, spaced 1-2 minutes apart, was used for the analysis. Blood was sampled at the start and end of each treatment period to measure a clinical chemistry panel including HbA1c, lipids, serum creatinine, potassium, albumin, haemoglobin and haematocrit. Urinary albumin and creatinine were assessed in first morning void urine samples. The geometric mean UACR values from the three first morning void urine samples were calculated at baseline and at the end of each treatment period.

2.3.2 | Bioimpedance spectroscopy

Bioimpedance spectroscopy was performed at the start and end of each treatment period with the Impedimed SFB7 device (ImpediMed Limited, Pinkenba, Australia) to assess changes in extracellular and intracellular volume, total body water and fat mass.[13]

2.3.3 | Kidney haemodynamic variables

Renal blood flow (RBF) was measured using two-dimensional (2D) magnetic resonance phase contrast imaging. The 2D phase contrast imaging was performed using electrocardiogram triggering and image acquisition in a plane perpendicular to each renal artery in a single breath-hold. Individual kidney RBF was calculated by integrating the flow velocity over the cardiac cycle times the cross-sectional area of the renal artery and the total RBF was calculated by adding the blood flow from each renal artery. Effective renal plasma flow (ERPF) was estimated by multiplying RBF by (1 – haematocrit). eGFR was calculated using the CKD Epidemiology Collaboration formula.[14] We calculated GFR in ml/min using the individual values of body surface area as estimated by the Du Bois and Du Bois equation.[15] The filtration fraction (FF) was obtained by dividing the calculated GFR by magnetic resonance imaging (MRI)-derived ERPF.

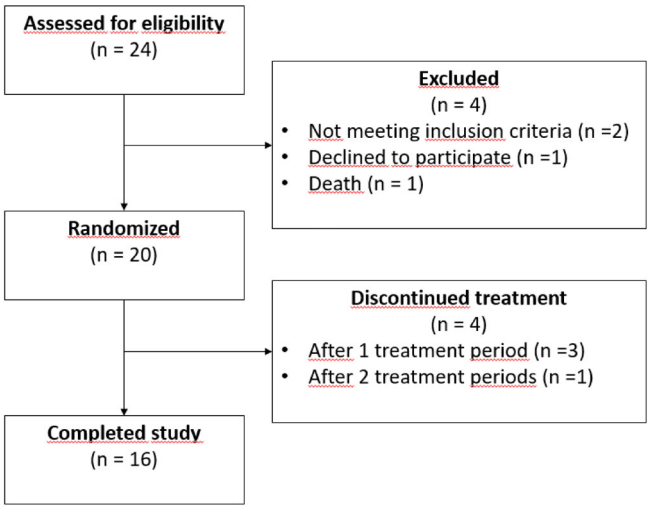

FIGURE 1 Patient disposition

2.4 | Outcome measures

The primary outcome was the percentage change from baseline (values measured at the start of each treatment period) in UACR. Secondary outcomes included change from baseline in BP, extracellular volume, fractional lithium excretion, kidney haemodynamic variables as determined by MRI (RBF, ERPF, FF) and correlation in albuminuria response during treatment with dapagliflozin, exenatide and dapagliflozin-exenatide combination. Investigator-reported adverse events and serious adverse events were monitored to assess safety.

2.5 | Statistical analysis

We calculated that 17 participants completing the study would provide at least 80% power to detect a reduction in UACR of 35% (i.e. delta = 0.43708 on the log-transformed albuminuria scale) or more with dapagliflozin and exenatide combination from baseline (alpha = 0.05) under the assumption of a within-subject standard deviation (SD) of 0.6 in log-transformed UACR. Assuming that approximately 10% of participants would discontinue the study prematurely, we enrolled 20 subjects.

TABLE 1 Baseline demographics

	N = 20
Age (y)	70.5 (± 5.1)
Sex (males)	16 (80%)
Race	
Caucasian	19 (95%)
Other	1 (5%)
Cardiovascular disease	2 (10%)
BMI (kg/m^2)	33.2 (± 4.3)
eGFR (ml/min/1.73m^2)	60.4 (± 18.8)
UACR (mg/mmol)	15.4 [4.1 to 518.4]
Haemoglobin (mmol/L)	8.4 (± 1.2)
Haematocrit (L/L)	0.4 (± 0.1)
HbA1c (%)	8.2 (± 1.3)
Systolic blood pressure (mmHg)	148.9 (± 15.3)
Diastolic blood pressure (mmHg)	75.9 (± 6.1)
Potassium (mmol/L)	4.3 (± 0.4)
Medication	
Metformin	11 (55%)
Insulin	15 (75%)
ACE inhibitor	9 (45%)
Angiotensin-receptor blocker	11 (55%)
Statin	11 (55%)

Note: Continuous variables are shown as mean (SD) or median [IQR].
Abbreviations: ACE, angiotensin-converting enzyme; BMI; body mass index, eGFR; estimated glomerular filtration rate, UACR; urinary albumin: creatinine ratio.

TABLE 2 Mean values and changes from baseline after 6 weeks in primary and secondary outcomes during treatment with dapagliflozin, exenatide or dapagliflozin-exenatide

	Dapagliflozin	Exenatide	Dapagliflozin/exenatide
Primary outcome			
UACR (mg/mmol)			
Baseline	20.5 (10.1-71.6)	42.3 (13.3-119.6)	37.3 (9.5-70.2)
Week 6	15.4 (7.14-58.35)	40.9 (14.4-67.4)	29.8 (8.7-42.1
Change from baseline (%) (95% CI)	-21.9 (-34.8, -6.4)	-7.7 (-23.5, 11.2)	-26.0 (-38.4, -11.0)
P value	.003	.246	< .001
Secondary outcomes			
eGFR (ml/min/1.73m^2)			
Baseline	61.6 (19.4)	58.0 (16.3)	55.5 (18.8)
Week 6	57.7 (18.6)	56.0 (15.2)	49.7 (17.6)
Change from baseline (95% CI)	-4.0 (-6.5, -1.5)	-2.1 (-4.6, 0.5)	-7.5 (-10.1, -5.0)
P value	.003	.104	< .001
Systolic BP (mmHg)			
Baseline	151.5 (14.4)	151.5 (12.6)	148.5 (17.3)
Week 6	145.4 (16.5)	151.2 (18.2)	137.7 (17.2)
Change from baseline (95% CI)	-5.5 (-12.6, 1.6)	-0.5 (-7.9, 6.9)	-10.4 (-17.8, -3.1)
P value	.124	.884	.008
HbA1c (mmol/mol)			
Baseline	7.9 (1.3)	8.1 (1.3)	7.9 (1.5)
Week 6	7.8 (1.3)	7.7 (1.0)	7.3 (1.1)
Change from baseline (95% CI)	-0.2 (-0.5, 0.1)	-0.4 (-0.8, -0.1)	-0.6 (-0.9, -0.2)
P value	.202	.015	.003
Body weight (kg)			
Baseline	100.8 (14.1)	102.0 (15.7)	101.3 (13.9)
Week 6	101.6 (13.9)	100.4 (14.0)	99.5 (13.6)
Change from baseline (95% CI)	-0.1 (-1.6, 1.3)	-1.7 (-3.2, -0.1)	-2.01 (-3.5, -0.5)
P value	.857	.034	.012
Haemoglobin (g/dl)			
Baseline	8.5 (1.1)	8.3 (1.2)	8.2 (1.4)
Week 6	8.5 (1.1)	8.3 (1.1)	8.5 (1.3)
Change from baseline (95% CI)	0.07 (-0,1, 0.3)	-0.04 (-0.2, 0.2)	0.22 (0.0, 0.4)
P value	.451	.677	.027
Haematocrit (%)			
Baseline	41.4 (4.6)	40.5 (5.5)	40.4 (6.2)
Week 6	41.9 (5.6)	40.5 (5.0)	42.2 (6.3)
Change from baseline (95% CI)	0.6 (-0.5, 1.7)	0.0 (-1.1, 1.1)	1.4 (0.3, 2.6)
P value	.277	.939	.015
Extracellular volume (L)			
Baseline	23.8 (4.4)	24.1 (4.4)	23.8 (4.0)
Week 6	25.0 (7.2)	23.8 (4.4)	22.8 (3.9)
Change from baseline (95% CI)	1.2 (-0.8, 3.2)	0.03 (-2.1, 2.2)	-0.98 (-3.0, 1.0)
P value	.216	.980	.320
Intracellular volume (L)			
Baseline	28.3 (4.0)	28.0 (4.0)	28.9
Week 6	29.3 (6.4)	27.7 (3.8)	29.0

(Continues)

TABLE 2 (Continued)

	Dapagliflozin	Exenatide	Dapagliflozin/exenatide
Change from baseline (95% CI)	1.1 (-1.5, 3.6)	0.01 (-2.8, 2.8)	0.6 (-1.9, 3.2)
P value	.402	.992	.606
Fat-free mass (kg)			
Baseline	71.1 (10.9)	71.1 (11.1)	72.1 (10.1)
Week 6	70.4 (10.0)	70.3 (10.9)	68.7 (10.2)
Change from baseline (95% CI)	-1.4 (-3.8, 0.9)	-0.4 (-2.9, 2.0)	-3.1 (-0.7, -2.7)
P value	.208	.710	.013
Fractional Li^+ excretion (%)			
Baseline	9.5 (6.4)	8.6 (8.3)	8.1 (8.1)
Week 6	12.6 (12.3)	10.1 (10.8)	7.1 (5.9)
Change from baseline (%) (95% CI)	22.6 (-7.2, 52.3)	1.8 (-27.4, 31.0)	15.7 (-17.7, 49.1)
P value	.120	.893	.314

Note: Baseline and week 6 values are shown as mean (SE) or median [IQR].
Note: The effects of dapagliflozin, exenatide or dapagliflozin-exenatide on the presented outcomes cannot be directly derived from the summary statistics because of the crossover design. Change from baseline for each variable is therefore obtained from a linear mixed effects model that included treatment and period as fixed effects.
Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; UACR; urinary albumin: creatinine ratio.

In case of premature study discontinuation, the data of completed treatment periods were included in the analyses.

Descriptive statistics were used to summarize baseline characteristics, which were presented as mean and SD for parametric data and as median and 25th and 75th percentile for non-parametric data. All analyses were performed in the intention-to-treat population. Linear mixed effects models were used to estimate the treatment effect of the three treatment strategies on the primary and secondary outcomes. The models included treatment and period as fixed effects. We used an unstructured covariance matrix for the random effects that allowed for correlated random effect and slopes for each participant across treatment periods. Carry-over effects were tested by adding a treatment × period interaction term to the relevant linear mixed effects models. Pearson correlation statistics were used to assess the correlation in UACR change from baseline among the three treatment strategies. Safety data are presented by treatment group for those participants who were randomized and had received at least one dose of study medication. All statistical analyses were performed with R (version 4.10; R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Baseline characteristics

From January 2019 to April 2021, 24 participants were assessed for eligibility, of whom 20 were enrolled in the study. During the study, four participants withdrew consent (Figure 1). One of these participants completed two treatment periods, while the other three participants completed one treatment period. The baseline characteristics of the randomized participants are shown in Table 1. Participants were predominantly male, with a mean age of 70.5 years and a body mass index of 33.2 kg/m^2. No changes in renin-angiotensin system–affecting medications occurred during the study, except for one participant, who switched from valsartan to an equivalent dose of losartan.

3.2 | Primary outcome: UACR

The median UACR at the start of treatment was 20.5 mg/mmol (IQR: 10.1 to 71.6) for dapagliflozin, 42.3 mg/mmol (IQR: 13.3 to 119.6) for exenatide and 37.3 mg/mmol (IQR: 9.5 to 70.2) for dapagliflozin-exenatide. After 6 weeks of treatment, the mean percentage change from baseline in UACR was −21.9% (95% CI: −34.8% to −6.4%) with dapagliflozin, −7.7% (95% CI: −23.5% to 11.2%) with exenatide and −26.0% (95% CI: −38.4% to −11.0%) with dapagliflozin-exenatide (*P* combination vs. dapagliflozin .582; *P* combination vs. exenatide .032; Table 2, Figure 2). At the end of the washout periods, UACR had increased relative to levels during the last on-treatment visit in the dapagliflozin and dapagliflozin-exenatide groups. In the exenatide group, however, UACR had further decreased at the end of washout (UACR change from baseline at the end of washout −23.5% [95% CI: −42.8% to 2.2%]). Although UACR did not return to baseline during exenatide treatment, carry-over effects were not detected (interaction treatment × period = 0.086).

There was considerable variation in UACR change from baseline among the individual participants in all three treatment groups. No association was found between UACR change during treatment with dapagliflozin and exenatide ($r = -0.33$; $P = .235$). There was also no correlation between UACR change during dapagliflozin-exenatide and dapagliflozin ($r = -0.099$; $P = .716$) or during dapagliflozin-exenatide and exenatide ($r = -0.45$; $P = .081$).

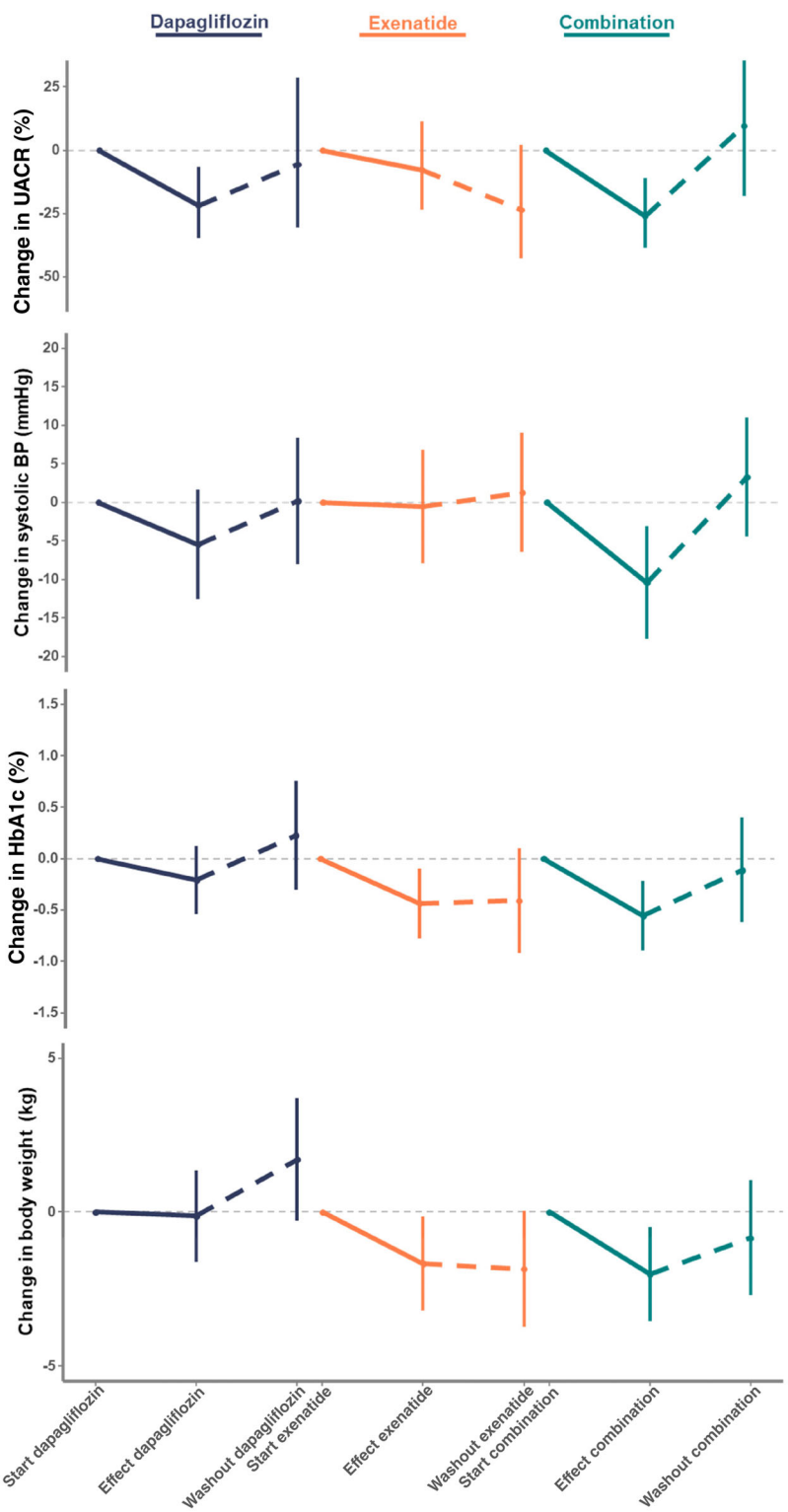

FIGURE 2 Changes in UACR, systolic BP, HbA1c and body weight during treatment with dapagliflozin, exenatide and dapagliflozin-exenatide. The error bars indicate the 95% confidence interval. The solid line indicates the change during treatment with dapagliflozin, exenatide or dapagliflozin-exenatide. The dashed line indicates the change during the washout period. BP, blood pressure; UACR, urinary albumin: creatinine ratio

3.3 | Secondary and exploratory outcomes

Mean systolic BP was 151.5 (SD 14.4) mmHg at the start of dapagliflozin, 151.5 (SD 12.6) mmHg at the start of exenatide and 148.5 (SD 17.3) mmHg at the start of dapagliflozin-exenatide. Systolic BP changed by −5.5 mm Hg (95% CI: −12.6 to 1.6) during dapagliflozin treatment, −0.5 mmHg (95% CI: −7.9 to 6.9) during exenatide treatment and −10.4 mmHg (95% CI: −17.8 to −3.1) during dapagliflozin-exenatide treatment (Table 2; Figure 2). Reductions in HbA1c and BW were observed during treatment with exenatide and dapagliflozin-exenatide, but not with dapagliflozin (Table 2; Figure 2). The observed effects on systolic BP, HbA1c and BW were numerically larger during dapagliflozin-exenatide treatment compared with dapagliflozin or exenatide alone. The effect on systolic BP, HbA1c and BW returned to baseline

values 9 weeks after discontinuation of dapagliflozin or dapagliflozin-exenatide, but persisted after exenatide discontinuation. Results from the linear mixed effects model showed that treatment with dapagliflozin and dapagliflozin-exenatide numerically increased fractional lithium clearance, whereas extracellular volume numerically decreased during combined dapagliflozin-exenatide treatment. Haematocrit increased during treatment with dapagliflozin-exenatide (Table 2).

3.4 | Kidney haemodynamic function

Mean eGFR was 61.6 (SD 19.4) ml/min/1.73m^2 at the start of dapagliflozin, 58.0 (SD 16.3) ml/min/1.73m^2 at the start of exenatide and 55.5 (SD 18.8) ml/min/1.73m^2 at the start of dapagliflozin-exenatide. After 6 weeks of treatment, the mean change in eGFR from baseline was −4.0 ml/min/1.73m^2 (95% CI: −6.5 to −1.5) during dapagliflozin treatment, −2.1 ml/min/1.73m^2 (95% CI: −4.6 to 0.5) during exenatide treatment and −7.5 ml/min/1.73 m^2 (95% CI: −6.2 to −5.0) during dapagliflozin-exenatide treatment (Table 2). The decrease in eGFR during dapagliflozin-exenatide differed significantly from that with monotherapy with either dapagliflozin ($P = .046$) or exenatide ($P = .0036$). The reduction in eGFR correlated with the reduction in UACR during the three treatment periods (Figure S1).

RBF and ERPF did not change with either monotherapy or combination therapy (Table 3; Figure 3). Although ERPF was not statistically significantly reduced, all but four and two patients in the combined dapagliflozin-exenatide and the dapagliflozin groups showed a reduction in ERPF, respectively. The FF did not statistically change during treatment with dapagliflozin and exenatide (Table 3; Figure 3). However, it decreased during dapagliflozin-exenatide treatment (−1.6% [95% CI: −3.2%, −0.01%]; $P = .048$).

3.5 | Safety

The study medication was generally well tolerated and the observed adverse events were consistent with those expected (Table 4). Mild hypoglycaemia occurred once with dapagliflozin and once with exenatide, but not with combined use. Gastrointestinal adverse events were more frequent during treatment with exenatide, whereas urinary tract infections occurred more frequently during treatment with dapagliflozin. One participant developed injection-site nodules during treatment with exenatide.

4 | DISCUSSION

In this randomized crossover trial in participants with type 2 diabetes and microalbuminuria or macroalbuminuria, 6 weeks of treatment with dapagliflozin statistically significantly reduced albuminuria from

TABLE 3 Mean values and changes from baseline after 6 weeks in MRI variables during treatment with dapagliflozin, exenatide or dapagliflozin-exenatide

	Dapagliflozin	Exenatide	Dapagliflozin/exenatide
eGFR (ml/min)[a]			
Baseline	69.4 (20.6)	68.7 (18.9)	63.5 (19.0)
Week 6	65.4 (20.3)	66.6 (18.0)	55.6 (15.7)
Change from baseline (95% CI)	-3.1 (-6.6, 0.3)	-2.2 (-5.8, 1.4)	-10.6 (-14.0, -7.2)
P value	.074	.212	< .001
Renal blood flow			
Baseline	856.6 (255.7)	895.8 (284.1)	870.5 (265.2)
Week 6	868.6 (277.4)	917.1 (323.4)	836.8 (301.8)
Change from baseline (95% CI)	-25.4 (52.5)	16.7 (54.7)	-16.5 (52.0)
P value	.636	.764	.755
Effective renal plasma flow			
Baseline	510.3 (155.5)	533.6 (155.4)	525.6 (151.5)
Week 6	510.5 (162.7)	548.0 (179.6)	499.9 (174.0)
Change from baseline (95% CI)	-19.6 (30.5)	14.5 (31.9)	-23.7 (30.1)
P value	.531	.655	.443
Filtration fraction (%)			
Baseline	14.4 (6.1)	13.6 (4.1)	12.7 (4.3)
Week 6	12.9 (4.6)	13.4 (5.7)	11.6 (3.4)
Change from baseline (95% CI)	0.0 (0.0)	-0.1 (0.8)	-1.6 (0.8)
P value	.977	.895	.048

Note: Changes from baseline for each variable are obtained from a linear mixed effects model that included treatment and period as fixed effects.
Abbreviations: eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging.
[a]eGFR not standardized by body surface area and expressed in ml/min. Baseline and week 6 values are shown as mean (SE).

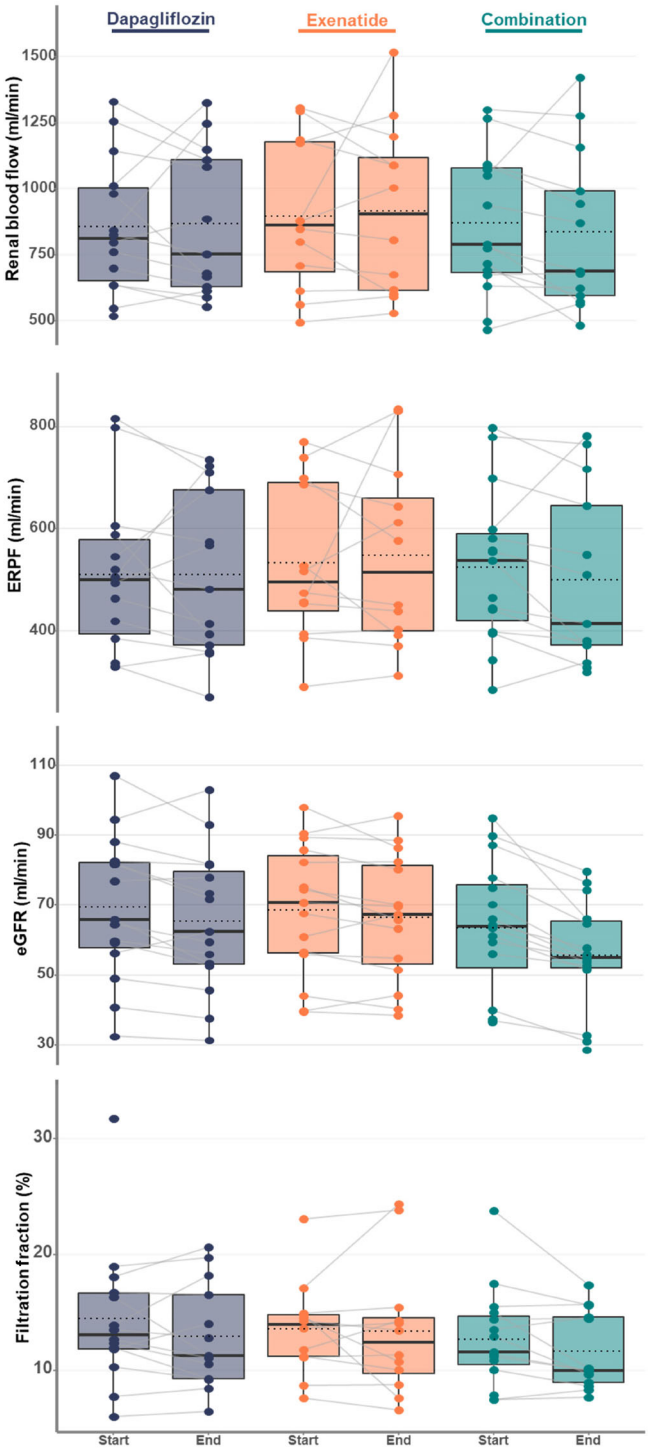

FIGURE 3 Changes in RBF, ERPF, eGFR and FF during treatment with dapagliflozin, exenatide and dapagliflozin-exenatide. The error bars indicate the 95% confidence interval. The solid horizontal black lines indicate the median and the dashed horizontal lines the mean. eGFR, estimated glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction; RBF, renal blood flow

baseline, while a modest non-significant reduction in albuminuria was observed during treatment with exenatide. Combined treatment with dapagliflozin and exenatide also statistically significantly reduced albuminuria from baseline with a numerically, but not statistically, larger reduction compared with either therapy alone. There was no correlation between albuminuria responses across treatment periods. In addition, dapagliflozin-exenatide consistently produced greater—albeit not statistically significant—reductions in systolic BP, BW and eGFR than monotherapy with either drug and was well tolerated.

GLP-1 RAs have been shown to reduce albuminuria in prior studies. A pooled analysis of six clinical trials showed that exenatide compared with control treatment reduced albuminuria by 26%.[16] The albuminuria-lowering effect was largely independent of concomitant changes in HbA1c and systolic BP, suggesting that the albuminuria-lowering efficacy was unlikely to be influenced by these changes. In a post hoc analysis from the EXCEL trial, exenatide compared with placebo reduced albuminuria by 28.2% among patients with type 2 diabetes and increased albuminuria.[17] The albuminuria reduction that was observed at the end of the 6-week treatment period in our crossover study was smaller compared with these prior studies, possibly because of the shorter follow-up in our study. In the previous clinical trials, the follow-up period was at least 24 weeks. Surprisingly, the UACR at the end of the washout period was further decreased compared with the end of the exenatide treatment period, and a similar persistence of effect of exenatide on eGFR, HbA1c and BW was observed. We do not have a clear explanation for this finding. Based on pharmacokinetic and pharmacodynamic modelling analysis, exenatide is not expected to be present in the systemic circulation after a washout period of 9 weeks. Moreover, other GLP-1 RAs showed that albuminuria rapidly reverses after treatment discontinuation, as shown in a study with liraglutide.[18] Notably, the persistent effect after washout was only seen with exenatide monotherapy, but not with exenatide-dapagliflozin.

SGLT2 inhibitors also reduce albuminuria in patients with type 2 diabetes and CKD. The DELIGHT study showed that dapagliflozin, compared with placebo, reduces albuminuria by 21%.[19] In the DAPA-CKD trial in 2906 patients with type 2 diabetes and CKD, dapagliflozin reduced albuminuria by 35%.[20] In both large clinical trials the albuminuria-lowering effect was fully present after 4 weeks of treatment and reversible 3 weeks after discontinuation of dapagliflozin. The mechanism by which dapagliflozin reduces albuminuria is not completely understood but an analysis from the DAPA-CKD trial showed that early reductions in eGFR strongly correlate with reductions in albuminuria, suggesting that the reduction in glomerular pressure through restoration of tubuloglomerular feedback reduces the glomerular leakage of albumin.[21] Similar findings were observed in the DECADE study, where the change in eGFR correlated with UACR change during all treatment periods.

Because the early reduction in albuminuria during treatment with GLP-1 RAs and SGLT2 inhibitors has been associated with reductions in the risk of kidney outcomes, combining both agents may be an attractive option to reduce the risk of kidney failure, in particular given that the mechanisms of action of both agents may be different and potentially additive. This notion is supported by data from clinical trials showing that the kidney-protective effect of SGLT2 inhibitors is present in both patients using and not using GLP-1 RAs.[22] Vice versa, the albuminuria-lowering and kidney-protective effect of GLP-1 RAs is present in patients regardless of concomitant SGLT2 inhibitor

TABLE 4 Number of participants with adverse events by treatment period

		Dapagliflozin (n = 18)	Exenatide (n = 17)	Dapagliflozin/ exenatide (n = 18)	Washout
Any adverse event, n		5	7	9	10
Serious adverse event, n		0	2	2	3
Adverse event, n					
Gastrointestinal	Constipation	0	1	1	0
	Diarrhoea	0	1	0	0
	Dyspepsia	0	1	1	0
	Haematochezia	1	0	0	0
	Nausea, vomiting	0	2	3	0
Endocrine	Hypoglycaemia	1	1	0	0
Infectious	Cold	0	0	0	3
	COVID-19	0	0	1	0
	Bronchitis	0	1	0	0
	Sepsis	0	0	1	0
	Urinary tract infection	2	0	0	0
Skin	Injection-site reaction	0	0	1	0
Other	Back pain	0	0	1	0
	Sore/burning feet	1	0	0	0

Abbreviation: COVID-19, Coronavirus Disease 2019.

use.[23] Although of interest, these studies did not assess if combined initiation of an SGLT2 inhibitor and a GLP-1 RA provides more kidney protection than either therapy alone. A clinical practice database reported regression in albuminuria stages associated with combined initiation of SGLT2 inhibitors and GLP-1 RAs. However, this study was a small non-randomized retrospective analysis and therefore prone to chance findings.[24] Another small post hoc analysis of a clinical trial in obese patients with type 2 diabetes tested this hypothesis. After 16 weeks, UACR decreased by 40% with dapagliflozin-exenatide, versus 18% with dapagliflozin, 16% with exenatide and 11% with placebo in obese patients with type 2 diabetes.[25] In the DECADE trial, the combination of exenatide and dapagliflozin also resulted in a numerically larger albuminuria reduction compared with either treatment alone, but the study was too small to draw definitive conclusions.

The effects of GLP-1 RAs and SGLT2 inhibitors on kidney haemodynamic function have been investigated in patients with type 2 diabetes and normal kidney function, but not in patients with lower eGFR or significant albuminuria.[26,27] The DECADE study showed that in these patients, eGFR modestly decreased along with modest reductions in ERPF and the FF during treatment with dapagliflozin and dapagliflozin-exenatide. An initial decline in eGFR is a well-known phenomenon after starting an SGLT2 inhibitor and the observed effects in the present trial are consistent with previous studies.[28,29] The mechanisms by how SGLT2 inhibitors modulate renal haemodynamics are not completely understood, but studies in patients with type 2 diabetes and preserved kidney function have suggested that dilation of postglomerular arterioles are probably involved in the haemodynamic effects of SGLT2 inhibitors.[27,30,31] Emerging data suggest that SGLT2 inhibitors can both constrict afferent arterioles and dilate efferent arterioles.[27,30] However, it should be noted that efferent postglomerular arterioles have smaller diameters than preglomerular arterioles. As a result, changes in the arterial diameter of postglomerular arterioles will have a larger impact on intraglomerular pressure than preglomerular arterial changes.[30]

Dapagliflozin and dapagliflozin-exenatide treatment increased fractional lithium clearance, suggesting that both agents, either through inhibition of SGLT2 or in the case of exenatide via inhibition of the sodium–hydrogen exchanger 3, inhibit proximal tubule sodium reabsorption.[32,33] Although these effects did not reach statistical significance, the magnitude of this effect was similar compared with other studies.[34,35] Extracellular volume numerically decreased during combined dapagliflozin-exenatide treatment, suggesting volume contraction, which may be attributed to increased natriuresis and diuresis, as both dapagliflozin and exenatide have been shown to induce natriuretic effects through blockade of the SGLT2 and sodium–hydrogen exchanger 3 transporter in the proximal tubule of the kidney. The statistically significant increase in haematocrit supports this notion, although haematocrit may also increase through direct effects on haematopoiesis during SLGT2 inhibition.

Our study has limitations, the most obvious being the small sample size and short follow-up, which precluded an assessment of the long-term effects of combined exenatide-dapagliflozin treatment and limited the precision of the effect estimates. Second, the study was powered to detect clinically relevant reductions in albuminuria within

each treatment group, but was not powered to determine between-group differences. In addition, for feasibility reasons, the study had an open-label design. Finally, no gold standard quantification of kidney haemodynamic function was performed, instead we used MRI-derived RBF and GFR derived from estimation equations, which may have affected the precision of our effect estimates. Despite these limitations, our results add to the growing body of evidence that supports combined use of a SGLT2 inhibitor and one GLP-1 RA.

In conclusion, dapagliflozin, exenatide and dapagliflozin-exenatide reduced albuminuria in participants with type 2 diabetes and microalbuminuria or macroalbuminuria. Larger, longer duration studies are warranted to provide more definitive evidence regarding the safety and efficacy of the combination of an SGLT2 inhibitor and GLP-1 RA.

AUTHOR CONTRIBUTIONS

ABvdA, DHvR, KH and HJLH designed the study. ABvdA, EA, DBR, IF, LJ, KH and HJLH collected the data. NJ performed statistical analyses. ABvdA and HJLH wrote the first draft of the manuscript. All authors contributed with revisions for important intellectual content. All authors approved the submission of the manuscript.

ACKNOWLEDGEMENTS

The authors thank all study participants, and the research staff that supported the conduct of the study. Study medication was kindly supplied by AstraZeneca.

CONFLICT OF INTEREST

ABvdA, EA, NJ and DBR have nothing to disclose. DHvR 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. CDS is employed by AstraZeneca. IF is employed by Antaros Medical AB. LJ is an employee and shareholder of Antaros Medical AB. KH has consulting relationships with Novo Nordisk and Sanofi, and receives research operating funding from Novo Nordisk. HJLH has consulting relationships with AstraZeneca, Bayer, Boehringer Ingelheim, CSL Behring, Chinook, Dimerix, Eli-Lilly Gilead, Janssen, Merck, Mitsubishi Tanabe, Mundi Pharma, Novo Nordisk, Novartis and Travere Therapeutics. He has received research support from AstraZeneca, Boehringer Ingelheim, Janssen and Novo Nordisk (all payments to his institution).

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.15033.

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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SUPPORTING INFORMATION

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How to cite this article: van der Aart-van der Beek AB, Apperloo E, Jongs N, et al. Albuminuria-lowering effect of dapagliflozin, exenatide, and their combination in patients with type 2 diabetes: A randomized cross-over clinical study. *Diabetes Obes Metab*. 2023;25(6):1758-1768. doi:10.1111/dom.15033