Renal Effects of DPP-4 Inhibitor Sitagliptin or GLP-1 Receptor Agonist Liraglutide in Overweight Patients With Type 2 Diabetes: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial

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OBJECTIVE

To investigate effects of dipeptidyl peptidase-4 inhibitor (DPP-4I) sitagliptin or glucagon-like peptide 1 (GLP-1) receptor agonist liraglutide treatment on renal hemodynamics, tubular functions, and markers of renal damage in overweight patients with type 2 diabetes without chronic kidney disease (CKD).

RESEARCH DESIGN AND METHODS

In this 12-week, randomized, double-blind trial, 55 insulin-naïve patients with type 2 diabetes (mean ± SEM: age 63 ± 7 years, BMI 31.8 ± 4.1 kg/m^2, glomerular filtration rate [GFR] 83 ± 16 mL/min/1.73 m^2; median [interquartile range]: albumin-to-creatinine ratio (ACR) 1.09 mg/mmol [0.47–3.31]) received sitagliptin (100 mg/day), liraglutide (1.8 mg/day), or matching placebos. GFR (primary end point) and effective renal plasma flow (ERPF) were determined by inulin and para-aminohippuric acid clearance, respectively. Intrarenal hemodynamic variables were estimated. Absolute and fractional excretions of sodium (FE_{Na}), potassium, and urea (FE_U) and renal damage markers (ACR, neutrophil gelatinase–associated lipocalin [NGAL], and kidney injury molecule-1 [KIM-1]) were measured. Plasma renin concentration (PRC) and glycated hemoglobin (HbA_{1c}) were assessed. At weeks 2 and 6, estimated GFR and fractional electrolyte excretions were determined.

RESULTS

At week 12, GFR was not affected by sitagliptin (−6 mL/min/1.73 m^2 [95% CI −14 to 3], $P = 0.17$) or liraglutide (+3 mL/min/1.73 m^2 [−5 to 11], $P = 0.46$), compared with placebo. Sitagliptin modestly reduced estimated glomerular hydraulic pressure (P_{GLO}; $P = 0.043$). ERPF, other intrarenal hemodynamic variables, renal damage markers, and PRC did not change for both treatments. Both agents reduced HbA_{1c}. Only at week 2, sitagliptin increased FE_{Na} and FE_U ($P = 0.005$).

CONCLUSIONS

Twelve-week treatment with sitagliptin or liraglutide does not affect measured renal hemodynamics. No sustained changes in tubular functions or alteration in renal damage markers were observed. The validity and clinical relevance of the slight sitagliptin-induced P_{GLO} reduction remains speculative.

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Driven by the relentless global obesity and diabetes pandemic, diabetic kidney disease (DKD) has become the leading cause of chronic kidney disease (CKD), resulting in end-stage kidney disease, cardiovascular events, and premature death (1). Prevention and treatment of DKD in type 2 diabetes focuses on early detection of albuminuria and decline of glomerular filtration rate (GFR) and control of renal risk factors, including hyperglycemia, obesity, systemic hypertension, glomerular hyperfiltration, albuminuria, and dislipidemia (1). As renin-angiotensin system (RAS) inhibitors exhibit blood pressure–independent benefits on renal outcome, these drugs are widely recommended for hypertension management in type 2 diabetes (1). However, despite intensified control of multiple risk factors, 25% of the patients with type 2 diabetes in the Steno-2 trial developed or progressed in their renal disease, and the rate of GFR decline was similar to conventional therapy (2). Interestingly, in Steno-2 and daily clinical practice (2,3), recommended targets are often not achieved, and as such, a single drug that targets various risk factors involved in the pathogenesis of DKD may lead to more salutary long-term renal outcomes.

Glucagon-like peptide 1 (GLP-1)–based therapies, i.e., dipeptidyl peptidase-4 inhibitors (DPP-4Is) and GLP-1 receptor agonists (GLP-1RAs), are widely used antihyperglycemic drugs in type 2 diabetes. Both drug classes improve pancreatic islet cell function by increasing insulin and reducing glucagon secretion but also display various extrapancreatic actions (1). Interestingly, in experimental models of diabetes and hypertension, GLP-1–based therapies prevented the onset and progression of renal disease as well as renal morphological abnormalities of DKD (4). In clinical trials, DPP-4Is (5–9) and GLP-1RAs (10–14) decrease the surrogate renal end point albuminuria in patients with type 2 diabetes, while the composite renal end point was reduced by 22% in the cardiovascular outcome trial of the GLP-1RA liraglutide (15). The finding that the albuminuria-lowering effect of the DPP-4I linagliptin is independent of changes in glycated hemoglobin (HbA_{1c}) suggests that mechanisms beyond glucose lowering are involved (16).

The glucose-independent renoprotective potential of GLP-1–based therapies in type 2 diabetes may be explained by their actions on several renal risk factors (1). As such, in patients with type 2 diabetes, DPP-4Is and GLP-1RAs decrease blood pressure (1) and improve lipid profiles, whereas GLP-1RA treatment reduces body weight (1). GLP-1 peptide infusion in obese hyperfiltrating males (25% of whom were diagnosed with type 2 diabetes) resulted in a reduction of creatinine clearance–measured glomerular hyperfiltration (17), which is closely associated with glomerular hydraulic pressure (P_{GLO}) (1). Moreover, the reduction in albuminuria at 7 weeks (18) and 1 year (13) of liraglutide treatment was paralleled by a decrease in GFR in an uncontrolled open-label study in patients with type 2 diabetes. However, other acute studies using GLP-1 or GLP-1RA in healthy males and patients with type 2 diabetes did not observe favorable responses on renal hemodynamics (19–24). Thus, the effects of DPP-4I or GLP-1RA treatment on renal hemodynamics remain incompletely understood.

In the current study, we determined the effects of prolonged (12-week) treatment with the DPP-4I sitagliptin or GLP-1RA liraglutide on GFR, effective renal plasma flow (ERPF), tubular functions, markers of renal damage, and renal risk factors in patients with type 2 diabetes without CKD. We hypothesized that GLP-1–based therapies reduce gold standard–measured GFR and estimated P_{GLO} in type 2 diabetes.

RESEARCH DESIGN AND METHODS

Trial Design

This was a phase 4, monocenter, randomized, double-blind, placebo-controlled, double-dummy, parallel-group, mechanistic intervention trial, as described previously (25). The study was approved by the ethics review board of the VU University Medical Center and local authorities. The study was registered at ClinicalTrials.gov (NCT01744236) and complied with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study Population

Patients were recruited by advertisements in local newspapers. The inclusion and exclusion criteria were previously reported (25). In short, eligible patients (aged 35–75 years) were Caucasian, were men or postmenopausal women with type 2 diabetes (HbA_{1c} 6.5–9.0% [48–75 mmol/mol]), had a BMI of 25–40 kg/m^2, and were treated with a stable dose of metformin and/or sulfonylurea for ≥3 months before enrollment. Key exclusion criteria included history of malignancy, pancreatic or active liver disease, estimated GFR (eGFR) <60 mL/min/1.73 m^2, current urinary tract infection, active nephritis, urinary retention (completeness of bladder emptying was assessed by bladder ultrasonography at screening visit), or use of diuretics that could not be stopped 3 months prior to and during the intervention period. All patients provided written informed consent before trial-related activities.

Intervention and Randomization

Patients were randomized 1:1:1, with a block size of six, by an independent trial pharmacist using computer-generated numbers (25). Patients and investigators remained blinded to treatment status until the last patient completed the last study visit and database lock. Patients received prefilled pens for subcutaneous injection containing visually identical liraglutide or placebo (Novo Nordisk A/S, Bagsværd, Denmark), in addition to visually identical encapsulated oral capsules (ACE Pharmaceutical, Zeewolde, the Netherlands) containing sitagliptin (Merck, Kenilworth, NJ) or placebo, both to be taken once daily in the evening. A dose increment schedule was used for the subcutaneous injections (week 1, 0.6 mg; week 2, 1.2 mg; weeks 3–12, 1.8 mg daily), and depending on drug tolerance, time between dose increments could be extended or the dose could be decreased at the investigator's discretion.

Study End Points

The primary end point was treatment-induced change in inulin clearance–measured GFR from baseline to week 12, compared with placebo (25). All other (intra)renal hemodynamic variables, tubular functions (i.e., tubular handling of sodium, potassium, urea, or hydrogen, urinary osmolality), and markers of renal damage were considered secondary or exploratory end points. Changes in eGFR, blood pressure, body weight, body water percentage, HbA_{1c}, blood and urinary glucose, insulin, lipid profiles, and plasma renin concentration (PRC) were also analyzed. All variables were measured at baseline and after 12 weeks of treatment. Additional measurements of

eGFR, blood pressure, and fractional electrolyte excretion were performed after 2 and 6 weeks of treatment.

Study Protocol

Patients were instructed to adhere to an average intake of sodium chloride (9–12 g/day) and protein (1.5–2.0 g/kg/day) 2 days prior to renal testing days, to abstain from vigorous physical activity and alcohol ingestion for ≥24 h, and not to use nicotine or caffeine for ≥12 h. After an overnight fast, patients consumed 500 mL of tap water before arriving at the clinical research unit at 07:30 A.M. With the exception of metformin and thyroid hormone replacement therapy, all morning medications were delayed. Participants assumed a semirecumbent position in a temperature-controlled room (23.0 ± 1.0°C), and a venous cannula was inserted into an antecubital vein of the dominant arm for infusion of the renal tracer substances and into an antecubital vein of the nondominant arm for venous blood sampling. Before the renal tests, urine was collected to measure sodium, potassium, urea, creatinine, albumin, neutrophil gelatinase–associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) (Supplementary Fig. 1). In addition, morning blood samples were taken to determine HbA_{1c}, plasma glucose, serum insulin, lipids (triglycerides, total cholesterol, HDL cholesterol [HDL-C], LDL cholesterol [LDL-C]), albumin, PRC, creatinine, and cystatin C. Subsequently, the renal tests commenced. A bolus of inulin (Inutest; Fresenius Kabi Austria GmbH, Graz, Austria) 45 mg/kg body weight and PAH (initially aminohippurate sodium "PAH" 20%; Merck, Whitehouse Station, NJ; but due to discontinued manufacturing of this product, we switched to 4-aminohippuric acid solution 20%; Bachem Distribution Services GmbH, Weil am Rhein, Germany) 6 mg/kg was infused over 10 min. For continuous infusion, inulin was administered at 22.5 mg/mg (target plasma concentration 250 mg/L) and PAH at 12.7 mg/min (target plasma concentration 20 mg/L). After 90 min of equilibration, urine was collected by spontaneous voiding every 45 min for two periods. Diuresis was induced by oral intake of 10 mL/kg (maximum 1,000 mL) tap water during equilibration, followed by an intake of 200 mL/h. Patients were permitted to be upright during voiding and encouraged to reach a subjective feeling of total bladder emptying. Blood samples were taken before and after each urine collection period. Sodium, potassium, urea, osmolality, pH, and glucose were measured in the second urine collection, and blood samples were analyzed for sodium, potassium, and urea before and after this collection period. Hematocrit was determined between two urine collection periods. Intravenous lines were flushed with 2 mL of 0.9% saline after blood sampling, and a 0.9% saline infusion rate of 10 mL/h was sustained throughout the testing day, corresponding to a total volume load of 38 mL and a sodium load of ~0.3 g during the renal tests. Body water percentage was assessed before the renal tests and in between the two urine collection periods, using a single-frequency bioelectrical impedance analyzer (Maltron BF-906; Maltron International Ltd., Essex, U.K.). Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate were measured at arrival at the clinical research unit and during the renal tests by an automated oscillometric device (Dinamap; GE Healthcare, Little Chalfont, U.K.) over the brachial artery of the nondominant arm. Measurements were performed in triplicate at 1–2-min intervals, and the mean of the last two measurements was used. After 2 and 6 weeks of treatment, patients arrived in the fasting state and delayed all morning medication, except for metformin. Blood pressure was measured at arrival at the clinical research unit. Blood, obtained by venipuncture, and urine was measured for sodium, potassium, urea, and creatinine at week 2, and cystatin C was only measured in blood. Creatinine was determined in blood at week 6.

Assays

All urine and blood samples obtained at baseline and after 12 weeks of treatment were analyzed for inulin and PAH, as previously described (24). Venous blood glucose was measured in all blood samples during the renal tests using a YSI-2300 STAT glucose analyzer (YSI Life Sciences, Yellow Springs, OH). Sodium, potassium, urea, osmolality, creatinine, HbA_{1c}, plasma glucose, and lipids were assayed at the Department of Clinical Chemistry at the VU University Medical Center by conventional methods (24). Insulin was measured using an immunometric assay (ADVIA Centaur-XP Immunoassay System; Siemens Healthcare, Erlangen, Germany). Urinary pH was determined by a hand-held VARIO 2V00 pH meter and SenTix-V electrode (Wissenschaftlich-Technische Werkstätten GmbH, Weilheim, Germany). Urine concentrations of NGAL and KIM-1 were determined by sandwich ELISA according to the manufacturer's specification (R&D Systems, Minneapolis, MN). PRC was determined with a commercial immunoradiometric kit (Renin III; Cisbio, Gif-sur-Yvette, France). Insulin resistance was estimated from fasting plasma glucose (FPG) and insulin, using the updated homeostatic model assessment-insulin resistance (HOMA2-IR) (https://www.dtu.ox.ac.uk/homacalculator).

Sample Size Calculation

Based on previous human data (17), we calculated that a sample size of 15 patients per treatment arm should be sufficient to detect a change in GFR of at least 15%, assuming an SD of 8 mL/min, $\alpha = 0.05$, and power ($1 - \beta$) of 80%. To allow for a dropout rate of 15% and increased power, we decided to include 20 patients per treatment arm (25).

Calculation of Renal Physiology and Markers of Kidney Damage

GFR and ERPF were calculated from inulin and PAH clearances, respectively, based on timed urine sampling, and the average of the two consecutive urine collection periods was used for analysis. Renal blood flow (RBF) was calculated as ERPF/(1 − hematocrit), filtration fraction (FF) as GFR/ERPF, and renal vascular resistance as MAP/RBF. Intrarenal hemodynamics (i.e., P_{GLO} and afferent and efferent arteriolar resistance [R_A and R_E, respectively]) were estimated according to the Gomez formulae (Supplementary Methods) (24). For eGFR, we used both the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 and creatinine-cystatin C CKD-EPI 2012 equations (accessed via www.kidney.org/professionals/kdoqi/gfr_calculator). Fractional sodium (FE_{Na}), potassium (FE_K), and urea (FE_U) excretion were calculated by using inulin as reference substance, unless stated otherwise. Absolute electrolyte excretion was calculated as urinary electrolyte

concentrations × urine flow. We calculated plasma osmolarity as 2[Na] + [urea] + [glucose], and osmol clearance by urine osmolality × urine flow/plasma osmolarity. Urine flow − osmol clearance was used to calculate free water clearance. Urinary albumin, NGAL, and KIM-1 were corrected for creatinine, and renal hemodynamic variables were corrected for body surface area using the Mosteller formula (24).

Data Management and Statistics

Data were double entered into an electronic data management system (OpenClinica LLC, version 3.3, Waltham, MA) and exported to the final study database. Before deblinding, urine collection periods characterized by profound collection errors, defined as an inulin extraction ratio of greater or less than one SD of the mean, were discarded from the analyses. Urine collection errors were present in eight patients (two randomized to placebo, four to sitagliptin, and two to liraglutide), in whom we calculated GFR and ERPF according to the continuous infusion method (26) and excluded urine flow–dependent end points. Statistical analyses were performed in the per protocol population using SPSS 22.0 (IBM SPSS Inc., Chicago, IL). Multivariable linear regression models were used for single measured end points and linear mixed models for repeated measured end points. In the multivariable regression model, the end point of interest was added as dependent variable, and treatment with sitagliptin or liraglutide were included as dummy variables (comparing sitagliptin vs. placebo and liraglutide vs. placebo). Corresponding baseline values were added as independent variable to correct for potential between-group differences at baseline. In the linear mixed model, treatments with sitagliptin or liraglutide were included as dummy variables, time as fixed factor, and intervention-by-time interaction was the parameter of interest. Data are presented as mean ± SEM or median with a two-sided 95% CI, unless stated otherwise. Between-group differences were tested at a two-sided α-level of 0.05.

RESULTS

Of the 94 patients screened between July 2013 and March 2015, 60 patients were included, of whom 56 were randomly assigned to treatments with placebo (n = 17), sitagliptin (n = 20), or liraglutide (n = 19) (Supplementary Fig. 2). Treatment discontinuation occurred in one patient in the sitagliptin group because of adverse events (dizziness and pollakiuria). Due to intolerance of a higher-dose liraglutide, one patient completed the study using liraglutide 0.6 mg daily. Baseline characteristics were similar among the three treatment groups (Table 1).

Primary End Point

Neither sitagliptin (−6 mL/min/1.73 m^2 [95% CI −14 to 3], P = 0.169) nor liraglutide (+3 mL/min/1.73 m^2 [−5 to 11], P = 0.464) affected GFR compared with placebo (Fig. 1*A*).

Secondary Renal End Points

ERPF tended to decrease after 12 weeks of treatment with sitagliptin (−37 [−74 to 0.6], P = 0.053) but did not change with liraglutide (P = 0.854) (Table 2). Only sitagliptin reduced P_{GLO} by 2.8 mmHg (−5.5 to −0.1, P = 0.043) and FE_U (P = 0.017). No changes in other (intra)renal hemodynamic variables or tubular functions were observed (Table 2). Neither treatment induced changes in albumin-to-creatinine ratio (ACR), NGAL, or KIM-1 (Table 2). Although eGFR was reduced after 2 weeks in all study groups, no changes of sitagliptin

Table 1—Baseline characteristics

Variables	Placebo (n = 17)	Sitagliptin (n = 19)	Liraglutide (n = 19)	All (n = 55)
Age (years)	65.8 ± 5.8	61.7 ± 6.8	60.5 ± 7.2	62.6 ± 6.9
Male, n (%)	13 (77)	16 (84)	14 (74)	43 (78)
Current smoker, n (%)	2 (12)	5 (26)	3 (16)	10 (18)
Weight (kg)	95.8 ± 9.8	99.4 ± 17.6	106.0 ± 17.2	100.6 ± 15.8
BMI (kg/m^2)	30.8 (28.9–31.5)	30.4 (28.2–35.9)	32.0 (30.9–35.9)	31.0 (28.3–33.6)
Diabetes duration (years)	8 (5–12)	6 (4–12)	7 (4–13)	6 (4–12)
HbA_{1c} (%)	7.5 ± 0.7	7.1 ± 0.5	7.4 ± 0.7	7.3 ± 0.6
HbA_{1c} (mmol/mol)	58 ± 8	54 ± 6	57 ± 7	56 ± 7
FPG (mmol/L)	8.9 ± 2.0	8.0 ± 0.9	8.3 ± 1.4	8.4 ± 1.5
HOMA2-IR	1.6 (1.3–2.7)	1.7 (1.2–2.8)	1.6 (1.0–2.4)	1.7 (1.2–2.4)
GFR (mL/min/1.73 m^2)	83 ± 19	87 ± 15	79 ± 14	83 ± 16
eGFR (CKD-EPI 2009) (mL/min/1.73 m^2)	86 ± 13	90 ± 12	90 ± 11	89 ± 12
eGFR (CKD-EPI 2012) (mL/min/1.73 m^2)	90 ± 15	92 ± 13	93 ± 12	92 ± 13
ACR (mg/mmol)*	1.13 (0.45–4.89)	1.10 (0.48–4.10)	1.00 (0.52–1.33)	1.09 (0.47–3.31)
SBP (mmHg)	137.6 ± 14.9	132.5 ± 12.4	136.6 ± 17.0	135.5 ± 14.8
DBP (mmHg)	76.4 ± 6.8	75.2 ± 7.4	77.0 ± 5.4	76.2 ± 6.5
MAP (mmHg)	99.1 ± 10.3	95.9 ± 9.1	97.1 ± 9.3	97.3 ± 9.5
Heart rate (bpm)	65 ± 9	63 ± 8	67 ± 9	65 ± 9
Metformin use, n (%)	15 (88)	18 (95)	19 (100)	52 (95)
Sulfonylurea use, n (%)	8 (47)	9 (47)	7 (37)	24 (44)
Antihypertensive medication use, n (%)	11 (65)	10 (53)	15 (79)	36 (66)
RAS inhibitor use, n (%)	11 (65)	9 (47)	15 (79)	35 (64)

Data are mean ± SD or median (interquartile range), unless stated otherwise. *Most patients had ACR <3 mg/mmol. In 14 patients, ACR was ≥3 mg/mmol (6 randomized to placebo, 6 to sitagliptin, and 2 to liraglutide).

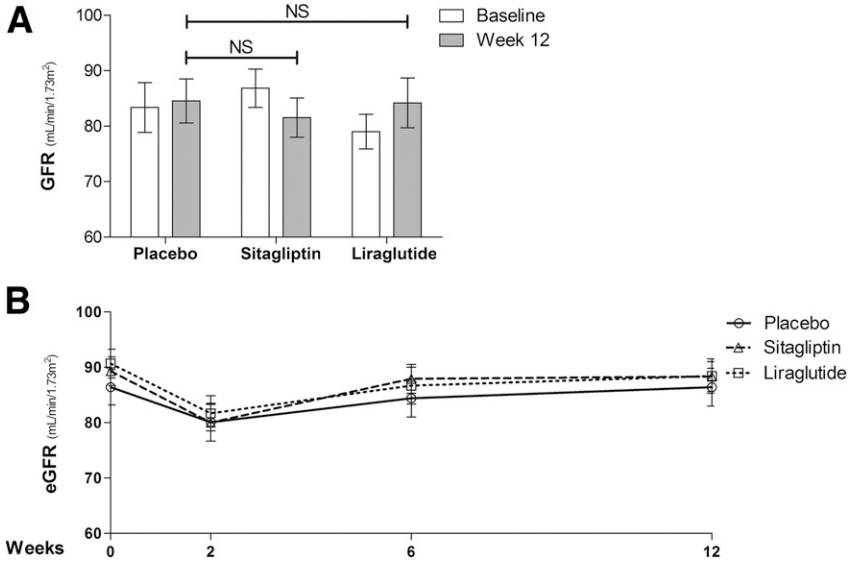

Figure 1—*A*: Mean ± SEM GFR at baseline and week 12. *B*: Mean ± SEM eGFR at weeks 0, 2, 6, and 12 using the CKD-EPI 2009 equation.

or liraglutide were observed at weeks 2 and 6 compared with placebo (Fig. 1*B* and Supplementary Fig. 3). Increases in creatinine-based FE_{Na} ($P = 0.005$) and FE_U ($P = 0.025$) were seen with sitagliptin at week 2 (Fig. 2) and returned to baseline after 12 weeks of study.

Blood Pressure, Body Weight, and Body Water

During the renal tests after 12 weeks of treatment, sitagliptin reduced SBP by 9 mmHg (95% CI −17 to −1, $P = 0.026$), and liraglutide reduced SBP by 8 mmHg (−17 to 0.03, $P = 0.051$), compared with placebo (Table 2). When blood pressure measurements at arrival at the clinical research unit were used, including values at weeks 2 and 6, only liraglutide reduced SBP by 13 mmHg (−22 to −3, $P = 0.008$) (Supplementary Fig. 4*A*–*C*). Moreover, sitagliptin tended to reduce body weight after 12 weeks (1.2 kg [−2.5 to 0.05], $P = 0.059$), whereas liraglutide reduced body weight after 6 weeks (1.7 kg [−3.0 to −0.5], $P = 0.009$) and 12 weeks (1.9 kg [−3.2 to −0.6], $P = 0.005$) (Supplementary Fig. 5). The treatments did not change body water percentage ($P > 0.05$) (Supplementary Table 1).

Glycemia, Insulin, Lipids, Plasma Albumin, and PRC

At week 12, mean reductions in HbA_{1c} from baseline, compared with placebo, were 0.8% (−9 mmol/mol) (−1.2 to −0.4 [−13 to −4], $P = 0.001$) for sitagliptin and 1.3% (−14 mmol/mol) (−1.7 to −0.9 [−19 to −9], $P < 0.001$) for liraglutide. FPG was reduced by both treatments ($P < 0.001$), whereas time-averaged mean blood glucose tended to decrease with sitagliptin (0.7 mmol/L [−1.4 to 0.05], $P = 0.067$) and decreased with liraglutide (1.3 mmol/L [−2.0 to −0.6], $P < 0.001$) during the renal tests (Supplementary Table 1). Baseline urinary glucose was <0.11 mmol/L in all but one patient (0.97 mmol/L) and did not change in response to treatment (data not shown). Fasting insulin increased with sitagliptin ($P = 0.020$) and liraglutide ($P < 0.001$). Liraglutide reduced HDL-C ($P = 0.036$), but other aspects of the lipid spectrum did not change. Plasma albumin levels were reduced with sitagliptin ($P = 0.020$) and liraglutide ($P = 0.008$). PRC did not change with either sitagliptin or liraglutide (Supplementary Table 1).

Sensitivity Analyses

Corrections for between-group differences in SBP or MAP, HbA_{1c}, time-averaged mean blood glucose, and fasting insulin concentrations did not affect treatment-induced changes in GFR. Likewise, when GFR was not indexed for body surface area, treatment-induced effects on GFR were still not different (Supplementary Fig. 6).

Safety

Both treatments were generally well tolerated. Adverse events of gastrointestinal origin were reported by 2 (11%) patients in the sitagliptin group, 12 (63%) patients in the liraglutide group, and 0 patients in the placebo group. Other adverse events (dermal, musculoskeletal, and nasopharyngeal) were rare, and occurrence was similar in all groups.

CONCLUSIONS

The current study is the first to investigate the effects of prolonged treatment with GLP-1–based therapies on gold standard–measured renal hemodynamics in patients with type 2 diabetes. Twelve-week treatment with sitagliptin or liraglutide does not affect GFR, ERPF, or other (intra)renal hemodynamic variables, although sitagliptin slightly reduced estimated P_{GLO}. In addition, sitagliptin increased creatine-based FE_{Na} and FE_U at week 2, which was not sustained after 12 weeks of treatment. Finally, renal damage markers are not affected by either sitagliptin or liraglutide.

The neutral effect of GLP-1–based therapy on GFR is in accordance with several randomized clinical trials of 12–30 weeks duration, in which DPP-4I or GLP-1RA treatment did not change (the slope of) creatinine-eGFR in patients with type 2 diabetes with (27–30) and without (5,29,31) renal impairment. However, as creatinine-based GFR estimates are generally inaccurate in patients with type 2 diabetes (1), renal clearance tests using exogenous tracers are needed to measure renal function. Acute intervention studies that used such tracers in healthy male participants also did not observe changes in GFR after GLP-1 peptide infusion (19,22), although acute exenatide infusion increased GFR, ERPF, and estimated P_{GLO} in overweight healthy males (21). Moreover, in patients with type 2 diabetes without CKD, acute administration of GLP-1 peptide (20), exenatide (24), or liraglutide (23) did not affect GFR. However, in obese insulin-resistant men with baseline glomerular hyperfiltration, acute GLP-1 peptide infusion reduced creatinine clearance (17), whereas prolonged liraglutide treatment reduced measured GFR in patients with type 2 diabetes with albuminuria and normal GFR (13,18).

Several mechanisms by which GLP-1–based therapies may affect renal hemodynamics have been proposed (1,32). GLP-1 (and associated therapies) could blunt the diabetes-associated proximal

Table 2—Comparison of renal and hemodynamic outcome measures between sitagliptin vs. placebo and liraglutide vs. placebo

	Placebo (n = 17)		Sitagliptin (n = 19)		Mean difference	Liraglutide (n = 19)		Mean difference
Variables	Baseline	Week 12	Baseline	Week 12	vs. placebo	Baseline	Week 12	vs. placebo
Renal hemodynamics								
ERPF (mL/min/1.73 m^2)	357 ± 25	373 ± 25	374 ± 19	349 ± 15	−37 (−74 to 0.6)	339 ± 17	363 ± 20	3 (−34 to 41)
RBF (mL/min/1.73 m^2)	611 ± 48	641 ± 50	654 ± 33	612 ± 25	−63 (−130 to 4)	576 ± 31	622 ± 38	10 (−58 to 77)
FF (%)	23.8 ± 0.6	23.2 ± 0.8	23.8 ± 0.9	23.6 ± 0.8	0.4 (−0.9 to 1.7)	23.7 ± 0.6	23.4 ± 0.7	0.3 (−1.0 to 1.6)
RVR (mmHg/L/min)	0.184 ± 0.013	0.179 ± 0.013	0.165 ± 0.008	0.173 ± 0.008	0.007 (−0.016 to 0.030)	0.176 ± 0.012	0.177 ± 0.011	−0.003 (−0.020 to 0.026)
Estimated variables								
P_{GLO} (mmHg)	61.0 ± 1.5	61.7 ± 1.3	61.4 ± 1.3	59.1 ± 1.3	−2.8 (−5.5 to −0.1)*	59.7 ± 1.1	62.0 ± 1.5	−0.4 (−3.1 to 2.3)
R_A (dyne · s · cm^{-5})	5,949 ± 677	6,001 ± 658	5,365 ± 424	5,839 ± 384	203 (−1,050 to 1,456)	5,638 ± 574	5,761 ± 615	−238 (−1,503 to 1,026)
R_E (dyne · s · cm^{-5})	3,969 ± 159	3,840 ± 178	3,802 ± 158	3,755 ± 140	63 (−189 to 315)	3,927 ± 124	3,859 ± 150	57 (−194 to 308)
Renal tubular functions								
FE_{Na} (%)	1.30 (0.91–1.34)	1.34 (0.66–1.97)	1.11 (0.89–1.41)	0.97 (0.54–1.47)	0.78 (0.52–1.16)§	1.14 (0.95–1.41)	1.04 (0.62–1.37)	0.75 (0.50–1.13)§
FE_K (%)	20 ± 1	20 ± 2	21 ± 1	20 ± 2	−2 (−7 to 3)	22 ± 2	22 ± 2	1 (−4 to 6)
FE_U (%)	65 (62–71)	67 (59–78)	69 (66–70)	56 (41–65)	0.75 (0.59–0.95)§*	73 (68–77)	69 (50–83)	0.99 (0.77–1.27)§
Na excretion (μmol/min/1.73 m^2)	121 ± 11	142 ± 22	150 ± 15	141 ± 20	−25 (−79 to 29)	137 ± 9	138 ± 18	−17 (−69 to 35)
K excretion (μmol/min/1.73 m^2)	57 ± 5	67 ± 6	72 ± 5	71 ± 7	−2 (−25 to 21)	67 ± 7	79 ± 10	8 (−14 to 30)
Urea excretion (μmol/min/1.73 m^2)	221 ± 13	208 ± 14	256 ± 21	191 ± 20	−31 (−86 to 24)	258 ± 29	260 ± 26	38 (−18 to 93)
Urinary pH	5.64 ± 0.14	5.61 ± 0.15	5.92 ± 0.14	5.76 ± 0.13	0.08 (−0.29 to 0.46)	5.98 ± 0.12	5.52 ± 0.14	−0.18 (−0.55 to 0.20)
Urine osmolality (mosmol/kg)	170 (121–241)	138 (114–182)	164 (134–225)	143 (114–259)	1.13 (0.87–1.45)§	154 (117–221)	139 (91–153)	0.81 (0.63–1.05)§
Urinary flow (mL/min/1.73 m^2)	5.6 ± 0.3	5.6 ± 0.3	5.4 ± 0.3	5.4 ± 0.4	−0.0 (−1.0 to 0.9)	5.0 ± 0.3	5.4 ± 0.4	0.2 (−0.7 to 1.1)
Osmolar clearance (mL/min/1.73 m^2)	2.2 (2.0–2.6)	2.5 (2.1–2.8)	2.6 (2.2–2.8)	2.6 (2.1–3.0)	1.02 (0.83–1.26)§	2.5 (1.8–2.9)	2.3 (1.7–2.9)	0.88 (0.72–1.09)§
Free water clearance (mL/min/1.73 m^2)	1.9 ± 0.4	2.4 ± 0.3	1.4 ± 0.6	2.2 ± 0.4	−0.4 (−1.4 to 0.7)	1.2 ± 0.9	2.7 ± 0.4	−0.0 (−1.0 to 1.0)
Renal damage								
ACR (mg/mmol)	1.13 (0.45–4.89)	2.12 (0.38–8.39)	1.10 (0.48–4.10)	0.89 (0.57–2.48)	0.68 (0.31–1.46)§	1.00 (0.52–1.33)	0.90 (0.46–1.24)	0.76 (0.35–1.64)§
NGAL (ng/mmol)	1,460 (773–2,363)	1,368 (686–2,095)	788 (620–2,072)	1,076 (835–2,555)	0.87 (0.51–1.51)§	1,400 (836–2,580)	919 (746–2,627)	0.94 (0.53–1.66)§
KIM-1 (ng/mmol)	84 (50–117)	62 (38–168)	113 (77–189)	110 (76–174)	1.31 (0.80–2.14)§	66 (47–128)	69 (62–214)	1.35 (0.83–2.19)§
Systemic hemodynamics								
SBP (mmHg)	145 ± 4	151 ± 4	140 ± 3	138 ± 3	−9 (−17 to −1)*	134 ± 4	136 ± 4	−8 (−17 to 0.03)
DBP (mmHg)	78 ± 2	80 ± 2	81 ± 2	81 ± 1	−1 (−5 to 3)	78 ± 2	80 ± 2	0 (−4 to 4)
MAP (mmHg)	102 ± 2	105 ± 2	103 ± 2	102 ± 2	−3 (−8 to 2)	98 ± 2	101 ± 2	−2 (−7 to 4)
Heart rate (bpm)	65 ± 2	65 ± 3	62 ± 2	62 ± 2	0 (−5 to 4)	66 ± 2	71 ± 2	5 (0.4–9)*

Data are mean ± SEM, median (interquartile range), or placebo and baseline-corrected mean difference (95% CI). RVR, renal vascular resistance. *$P < 0.05$; §Placebo and baseline-corrected ratio (95% CI).

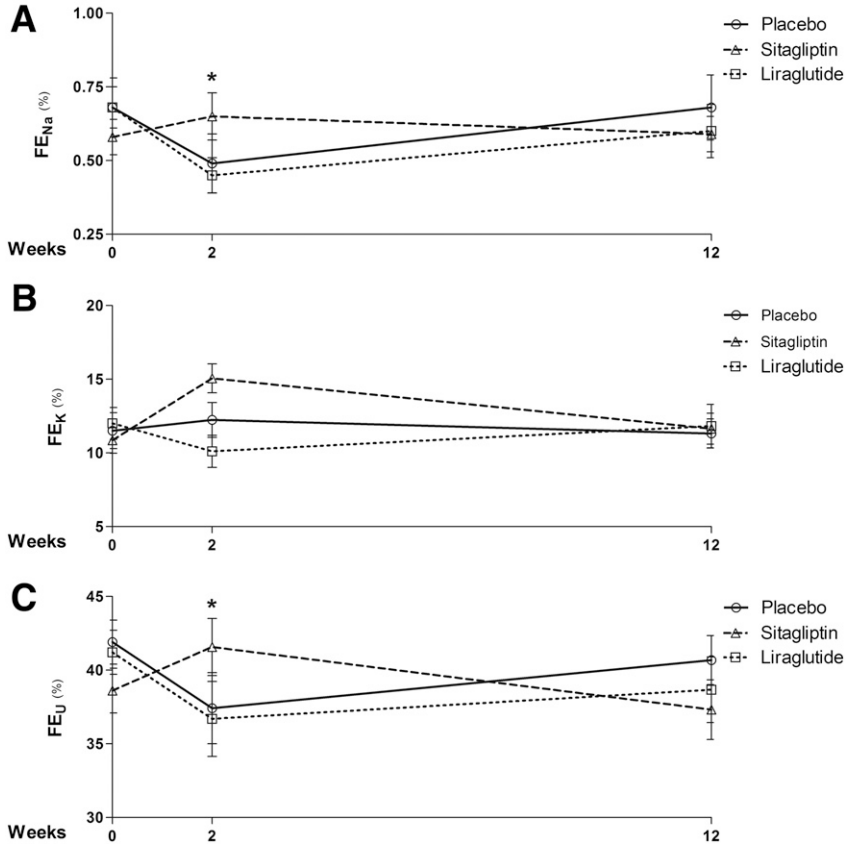

Figure 2—Mean ± SEM creatinine-based fractional electrolyte excretions at weeks 0, 2, and 12. *A*: Sodium. *B*: Potassium. *C*: Urea. *$P < 0.05$ vs. placebo at the given time point.

sodium hyper-reabsorption by reducing the activity of the sodium-hydrogen exchanger-3 (NHE3), which is coupled to a complex that also contains DPP-4, in the proximal tubule (1,4). By the increase in NaCl delivery to the macula densa, the subsequently activated TGF induces vasoconstriction of R_A, thereby potentially reducing P_{GLO} and (single-nephron) GFR (1,4). Numerous acute intervention studies have shown that GLP-1 and GLP1-RA increase proximal sodium excretion (17,21–24), and it was recently found that natriuresis was elevated after 3 weeks of liraglutide treatment (33). Intriguingly, in the current study, neither drug affected sodium excretion or diuresis after 12 weeks of treatment, although FE_{Na} transiently increased after 2 weeks of sitagliptin treatment. Possibly, GLP-1-based therapy–associated inhibition of NHE3 induces an initial period of negative sodium balance and fall in extracellular volume, which, as with classical diuretics, is subsequently counterbalanced by other factors, such as neurohumoral- and flow-mediated increases in tubular reabsorption (34). This may, among others (35,36), explain the blood pressure–lowering effects of these drugs, which in itself are unlikely to have affected renal hemodynamics in the current study as autoregulatory functions are apparently intact in patients without CKD. However, in conflict with this chain of events, recent studies using validated antibodies could not demonstrate the GLP-1 receptor in the proximal tubule (37), while only a minor portion of liraglutide-related metabolites passes the glomerular membrane (23), indicating that direct effects on renal NHE3 are unlikely. Potentially, transient natriuretic effects of GLP-1–based therapies are related to initial (modest) blood pressure increases (21,24), i.e., pressure natriuresis, or reductions in angiotensin-II (23,32). Reductions in renin release could also lead to reductions in GFR and P_{GLO} by reducing angiotensin-II–mediated vasoconstriction of the R_E. However, we did not observe changes in PRC. Interestingly, although R_A or R_E were not affected, P_{GLO} was somewhat reduced with sitagliptin, which may point toward a renoprotective hemodynamic effect, but might also be the result of concurrent small reductions in GFR and albumin used in the Gomez formula to calculate this parameter. Notably, a decrease in plasma protein concentration decreases the ultrafiltration coefficient in order to maintain stable GFR (38), but the Gomez estimation does not include this adaptation. Finally, obesity per se has also been associated with glomerular hyperfiltration (1). We observed reductions in body weight without effects on body water percentage in the liraglutide group, which may imply the absence of successive decreases in absolute body water, cardiac output, ERPF, and GFR.

Long-term studies in type 2 diabetes indicate that GLP-1–based therapies decrease albuminuria, at least partly independent of their glucose-lowering effects (5,7–14,18). Furthermore, it has been suggested that the liraglutide-induced benefits on renal outcome in the recent Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial could be due to improvements in renal risk factors, including renal hemodynamics (15). Indeed, we observed favorable effects on glycemia and several other renal risk factors, such as blood pressure and body weight, whereas glomerular filtration and dislipidemia were seemingly unaffected. However, ACR and other markers of renal damage did not improve, which could be due to the relative short duration of follow-up and/or the low level of renal damage in the current population at baseline.

Based on our and previous studies, one could speculate that the effects of GLP-1–based therapies on renal hemodynamics depend on treatment duration, hyperfiltration status (at the whole-kidney or single-nephron level), and other population-specific differences. First, potential acute effects could have returned toward baseline after long-term treatment due to receptor tachyphylaxis or compensatory mechanisms. Interestingly, a transient reduction in eGFR after 2 weeks was observed in our study. However, as this small initial fall in eGFR also occurred in the placebo group, the clinical significance of this observation is uncertain. Second, GLP-1–based therapies may reduce GFR in the setting of glomerular hyperfiltration at the whole-kidney level (defined as GFR >125–140 mL/min/1.73 m^2) (1,17). Moreover,

one could speculate that GLP-1–based therapies also reduce GFR in patients with microalbuminuria or renal impairment, who are more likely to exhibit compensatory hyperfiltration at the single-nephron level due to reduced nephron numbers (1,13,18). Although the mean FF of 23.7% in the current study is indicative of the presence of glomerular hyperfiltration, as it is well above the 17.7% normally found in healthy young adults (39), whole-kidney GFR was (only) mildly decreased (<90 mL/min/1.73 m^2) and ACR was not increased. Possibly, GLP-1–based therapies do not uniformly affect GFR in a population with type 2 diabetes with varying disease duration and potentially a more heterogeneous phenotype, as was the fact in the current trial. Finally, GLP-1–based therapies may not have relevant TGF-mediated effects in patients with type 2 diabetes, or their effect on (intra)renal hemodynamics is blunted by concomitant effects of the extensive use of RAS inhibitors in the current trial, which are known to reduce P_{GLO} and (single-nephron) hyperfiltration by reducing R_E (1,4). Notably, the relatively low PRC corresponds with other populations with diabetes and also does not indicate excessive RAS blockade (40).

This study has several limitations that need to be mentioned. First, confounding effects of glucose lowering or hormonal differences (e.g., insulin and glucagon) cannot be excluded since we did not perform clamp techniques during the renal tests. However, the current trial aimed to assess real-life effects. Second, formulas to estimate intrarenal hemodynamic variables necessitate assumptions. Third, although the current study was adequately powered to assess our hypothesis, there was not sufficient power to assess the effects in subpopulations, including patients with higher GFR, FF, or albuminuria at baseline. Fourth, the follow-up was relatively short, which may impede generalization to longer treatment periods. Nevertheless, we feel that the current study was sufficient to address all of the most likely mechanisms by which GLP-1–based therapies may affect renal hemodynamics, and, therefore, we speculate that longer treatment would not substantially change our findings.

In conclusion, 12-week treatment with sitagliptin or liraglutide has no effect on gold standard–measured renal hemodynamics in overweight patients with type 2 diabetes without CKD. However, sitagliptin modestly decreased estimated P_{GLO}, of which the validity and clinical relevance remains speculative. Furthermore, sitagliptin increased sodium excretion, although this did not sustain after 12 weeks. Our results indicate that the potential glucose-independent renoprotective effects of GLP-1–based therapy may not be explained by (intra)renal hemodynamic improvements but likely relate to benefits on other renal risk factors, such as blood pressure and body weight. Clinical trials with predefined (hard) renal end points are needed to determine whether GLP-1–based therapies confer renoprotection in patients with type 2 diabetes, and the use of active comparators in such studies (NCT01243424) may establish effects beyond glucose lowering.

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References

1. Muskiet MH, Tonneijck L, Smits MM, Kramer MH, Heerspink HJ, van Raalte DH. Pleiotropic effects of type 2 diabetes management strategies on renal risk factors. Lancet Diabetes Endocrinol 2015;3:367–381
2. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591
3. Vazquez-Benitez G, Desai JR, Xu S, et al. Preventable major cardiovascular events associated with uncontrolled glucose, blood pressure, and lipids and active smoking in adults with diabetes with and without cardiovascular disease: a contemporary analysis. Diabetes Care 2015;38:905–912
4. Muskiet MH, Smits MM, Morsink LM, Diamant M. The gut-renal axis: do incretin-based agents confer renoprotection in diabetes? Nat Rev Nephrol 2014;10:88–103
5. Cooper ME, Perkovic V, McGill JB, et al. Kidney disease end points in a pooled analysis of individual patient-level data from a large clinical trials program of the dipeptidyl peptidase 4 inhibitor linagliptin in type 2 diabetes. Am J Kidney Dis 2015;66:441–449
6. Goldshtein I, Karasik A, Melzer-Cohen C, et al. Urinary albumin excretion with sitagliptin compared to sulfonylurea as add on to metformin in type 2 diabetes patients with albuminuria: a real-world evidence study. J Diabetes Complications 2016;30:1354–1359
7. Hattori S. Sitagliptin reduces albuminuria in patients with type 2 diabetes. Endocr J 2011;58:69–73
8. Kawasaki I, Hiura Y, Tamai A, et al. Sitagliptin reduces the urine albumin-to-creatinine ratio in type 2 diabetes through decreasing both blood pressure and estimated glomerular filtration rate. J Diabetes 2015;7:41–46
9. Sakata K, Hayakawa M, Yano Y, et al. Efficacy of alogliptin, a dipeptidyl peptidase-4 inhibitor, on glucose parameters, the activity of the advanced glycation end product (AGE) - receptor for AGE (RAGE) axis and albuminuria in Japanese type 2 diabetes. Diabetes Metab Res Rev 2013;29:624–630
10. Bergenstal RM, Wysham C, Macconell L, et al.; DURATION-2 Study Group. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet 2010;376:431–439
11. Imamura S, Hirai K, Hirai A. The glucagon-like peptide-1 receptor agonist, liraglutide, attenuates the progression of overt diabetic nephropathy in type 2 diabetic patients. Tohoku J Exp Med 2013;231:57–61
12. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in patients with

type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–2257
13. von Scholten BJ, Hansen TW, Goetze JP, Persson F, Rossing P. Glucagon-like peptide 1 receptor agonist (GLP-1 RA): long-term effect on kidney function in patients with type 2 diabetes. J Diabetes Complications 2015;29:670–674
14. Zavattaro M, Caputo M, Samà MT, et al. One-year treatment with liraglutide improved renal function in patients with type 2 diabetes: a pilot prospective study. Endocrine 2015;50:620–626
15. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
16. Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, von Eynatten M. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes Care 2013;36:3460–3468
17. Gutzwiller JP, Tschopp S, Bock A, et al. Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. J Clin Endocrinol Metab 2004;89:3055–3061
18. von Scholten BJ, Lajer M, Goetze JP, Persson F, Rossing P. Time course and mechanisms of the antihypertensive and renal effects of liraglutide treatment. Diabet Med 2015;32:343–352
19. Asmar A, Simonsen L, Asmar M, et al. Renal extraction and acute effects of glucagon-like peptide-1 on central and renal hemodynamics in healthy men. Am J Physiol Endocrinol Metab 2015;308:E641–E649
20. Asmar A, Simonsen L, Asmar M, et al. Glucagon-like peptide-1 does not have acute effects on central or renal hemodynamics in patients with type 2 diabetes without nephropathy. Am J Physiol Endocrinol Metab 2016;310:E744–E753
21. Muskiet MH, Tonneijck L, Smits MM, et al. Acute renal haemodynamic effects of glucagon-like peptide-1 receptor agonist exenatide in healthy overweight men. Diabetes Obes Metab 2016;18:178–185
22. Skov J, Dejgaard A, Frøkiær J, et al. Glucagon-like peptide-1 (GLP-1): effect on kidney hemodynamics and renin-angiotensin-aldosterone system in healthy men. J Clin Endocrinol Metab 2013;98:E664–E671
23. Skov J, Pedersen M, Holst JJ, et al. Short-term effects of liraglutide on kidney function and vasoactive hormones in type 2 diabetes: a randomized clinical trial. Diabetes Obes Metab 2016;18:581–589
24. Tonneijck L, Smits MM, Muskiet MH, et al. Acute renal effects of the GLP-1 receptor agonist exenatide in overweight type 2 diabetes patients: a randomised, double-blind, placebo-controlled trial. Diabetologia 2016;59:1412–1421
25. Smits MM, Tonneijck L, Muskiet MH, et al. Cardiovascular, renal and gastrointestinal effects of incretin-based therapies: an acute and 12-week randomised, double-blind, placebo-controlled, mechanistic intervention trial in type 2 diabetes. BMJ Open 2015;5:e009579
26. Schnurr E, Lahme W, Küppers H. Measurement of renal clearance of inulin and PAH in the steady state without urine collection. Clin Nephrol 1980;13:26–29
27. Arjona Ferreira JC, Marre M, Barzilai N, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care 2013;36:1067–1073
28. Davies MJ, Bain SC, Atkin SL, et al. Efficacy and safety of liraglutide versus placebo as add-on to glucose-lowering therapy in patients with type 2 diabetes and moderate renal impairment (LIRA-RENAL): a randomized clinical trial. Diabetes Care 2016;39:222–230
29. Groop PH, Del Prato S, Taskinen MR, et al. Linagliptin treatment in subjects with type 2 diabetes with and without mild-to-moderate renal impairment. Diabetes Obes Metab 2014;16:560–568
30. McGill JB, Sloan L, Newman J, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study. Diabetes Care 2013;36:237–244
31. Tuttle KR, Heilmann C, Hoogwerf BJ, Brown C, Anderson PW. Effects of exenatide on kidney function, adverse events, and clinical end points of kidney disease in type 2 diabetes. Am J Kidney Dis 2013;62:396–398
32. Tonneijck L, Muskiet MH, Smits MM, van Raalte DH, Diamant M. Combining incretin-based drugs and RAAS inhibitors: more cons than pros? Lancet Diabetes Endocrinol 2014;2:684–685
33. Lovshin JA, Barnie A, DeAlmeida A, Logan A, Zinman B, Drucker DJ. Liraglutide promotes natriuresis but does not increase circulating levels of atrial natriuretic peptide in hypertensive subjects with type 2 diabetes. Diabetes Care 2015;38:132–139
34. Bock HA, Stein JH. Diuretics and the control of extracellular fluid volume: role of counterregulation. Semin Nephrol 1988;8:264–272
35. Foster MC, Hwang SJ, Porter SA, Massaro JM, Hoffmann U, Fox CS. Fatty kidney, hypertension, and chronic kidney disease: the Framingham Heart Study. Hypertension 2011;58:784–790
36. Lovshin JA, Zinman B. Blood pressure-lowering effects of incretin-based diabetes therapies. Can J Diabetes 2014;38:364–371
37. Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology 2014;155:1280–1290
38. Pollak MR, Quaggin SE, Hoenig MP, Dworkin LD. The glomerulus: the sphere of influence. Clin J Am Soc Nephrol 2014;9:1461–1469
39. Rabelink TJ, Koomans HA, Boer WH, van Rijn J, Dorhout Mees EJ. Lithium clearance in water immersion-induced natriuresis in humans. J Appl Physiol (1985) 1989;66:1744–1748
40. Hollenberg NK, Fisher ND, Nussberger J, Moukarbel GV, Barkoudah E, Danser AH. Renal responses to three types of renin-angiotensin system blockers in patients with diabetes mellitus on a high-salt diet: a need for higher doses in diabetic patients? J Hypertens 2011;29:2454–2461