Title
Impaired incretin homeostasis in non-diabetic moderate to severe chronic kidney disease

Authors
Ahmadi, Armin
Gamboa, Jorge
Norman, Jennifer E
et al.

Publication Date
2024-11-01

DOI
10.2215/cjn.0000000000000566

OPEN

Impaired Incretin Homeostasis in Nondiabetic Moderate-to-Severe CKD

Armin Ahmadi,[1] *Jorge Gamboa*,[2] *Jennifer E. Norman*,[3] *Bamba Enkhmaa*,[4] *Madelynn Tucker*,[5] *Brian J. Bennett*,[6] *Leila R. Zelnick*,[7] *Sili Fan*,[8] *Lars F. Berglund*,[9] *Talat Alp Ikizler*,[10] *Ian H. de Boer*,[7] *Bethany P. Cummings*,[5,11] and *Baback Roshanravan*[1]

Key Points

- Total incretin levels and incretin response during oral glucose tolerance testing were significantly higher among patients with moderate-to-severe nondiabetic patients with CKD compared with healthy people.
- Unlike in healthy individuals, increased incretin response was not correlated with insulin response and coincided with persistently greater glucagon levels to oral glucose tolerance testing in CKD.
- Disruption in the incretin system and glucagon dynamics may contribute to metabolic complications in moderate-to-severe CKD.

Abstract

Background Incretins are regulators of insulin secretion and glucose homeostasis metabolized by dipeptidyl peptidase-4 (DPP-4). CKD may modify incretin release, metabolism, or response.

Methods We performed 2-hour oral glucose tolerance testing in 59 people with nondiabetic CKD (eGFR <60 ml/min per 1.73 m^2) and 39 matched controls. We measured total area under the curve and incremental area under the curve (iAUC) of plasma total glucagon-like peptide-1 (GLP-1) and total glucose-dependent insulinotropic polypeptide (GIP). Fasting DPP-4 levels and activity were measured. Linear regression was used to adjust for demographic, body composition, and lifestyle factors.

Results Mean (SD) eGFR was 38±13 and 89±17 ml/min per 1.73 m^2 in patients with CKD and controls, respectively. GLP-1 total area under the curve and GIP iAUC were higher in patients with CKD than controls with a mean of 1531±1452 versus 1364±1484 pM×min and 62,370±33,453 versus 42,365±25,061 pg×min/ml, respectively. After adjustment, CKD was associated with 15,271 pM×min/ml greater GIP iAUC (95% confidence intervals [CIs], 387 to 30,154) compared with controls. Adjustment for covariates attenuated associations of CKD with higher GLP-1 iAUC (adjusted difference, 122; 95% CI, −619 to 864). Plasma glucagon levels were higher at 30 minutes (mean difference, 1.6; 95% CI, 0.3 to 2.8 mg/dl) and 120 minutes (mean difference, 0.84; 95% CI, 0.2 to 1.5 mg/dl) in patients with CKD compared with controls. There were no differences in insulin levels or plasma DPP-4 activity or levels between groups.

Conclusions Overall, incretin response to oral glucose is preserved or augmented in moderate-to-severe CKD, without apparent differences in circulating DPP-4 concentration or activity. However, neither insulin secretion nor glucagon suppression is enhanced.

CJASN ■: 1–11, 2024. doi: https://doi.org/10.2215/CJN.0000000000000566

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Received: February 15, 2024 **Accepted:** October 3, 2024
Published Online Ahead of Print: November 1, 2024

A.A., J.G., B.P.C., and B.R. contributed equally to this work.

Correspondence: Dr. Armin Ahmadi, email: arahmadi@ucdavis.edu

Introduction

CKD even in a nondiabetic setting is associated with metabolic dysregulation, including disrupted insulin and glucose homeostasis.[1–3] Factors contributing to CKD-associated glucometabolic complications include increased inflammation[4] and hyperglucagonemia.[5] Dysglycemia is a component of cardiovascular kidney metabolic syndrome linked to adverse cardiovascular and kidney disease outcomes.[6] CKD augments inflammation and disrupts lipid and glucose metabolism accelerating atherosclerosis and increasing cardiovascular risk.[7] Mechanistic studies demonstrate that CKD is associated with impaired insulin signaling and increased proteolysis through inflammatory signaling contributing to impaired glucose homeostasis.[8] However, there is limited understanding of how CKD affects incretin secretion known to influence glucose and insulin homeostasis.

Incretin hormones are secreted by the gut in response to nutrient intake and promote glucose-stimulated insulin secretion.[9] The two main incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) secreted by the enteroendocrine L and K cells, respectively.[10,11] GLP-1 and GIP account for up to 70% of postprandial insulin secretion (incretin effect) in healthy individuals.[12] Little is known about the independent effect of CKD on the secretion and response to incretins. However, incretins have opposing effects on glucagon secretion with GLP-1 suppression[13] and GIP-stimulating glucagon secretion.[14] In addition, understanding the impact of CKD on dipeptidyl peptidase-4 (DPP-4), a ubiquitous enzyme inactivating incretin hormones, is lacking.[15]

This study investigates postprandial incretin hormone levels and their determinants using a standardized oral glucose tolerance testing (OGTT) comparing nondiabetic patients with CKD and controls. We first describe the association of the presence and severity of kidney disease with circulating concentrations of incretin hormones in both fasted and postprandial states. We separately investigate the association of postprandial circulating incretin hormones with insulin, C-peptide, and glucagon levels during an OGTT by CKD status. We hypothesized that nondiabetic CKD is associated with heightened incretin hormone release and an impaired incretin effect contributing to glucometabolic complications in CKD.

Methods

Study Population and Study Design

The Study of Glucose and Insulin in Renal Disease is a cross-sectional study of moderate-to-severe nondiabetic CKD. Participants were recruited from nephrology and primary care clinics affiliated with the University of Washington and nearby institutions in Seattle, WA. From this population, a total of 98 participants were recruited for this study, among which 59 had CKD (eGFR <60 ml/min per 1.73 m^2) and 39 were controls (eGFR >60 ml/min per 1.73 m^2), and they had spot urine albumin-to-creatinine ratios <30 mg/g, frequency matched on age, sex, and race. Eligibility was determined at the screening visit, when eGFR was calculated from serum creatinine measured at a clinical laboratory. Exclusion criteria for both groups included age younger than 18 years, clinical diagnosis of diabetes mellitus, maintenance dialysis or fistula in place, history of kidney transplantation, use of medications known to reduce insulin sensitivity, fasting serum glucose ≥126 mg/dl, and hemoglobin<10 g/dl. A more detailed description of the study design, recruitment, and enrollment has been published previously.[3,16] The study was approved by the University of Washington Human Subjects Division. All participants provided written informed consent.

CKD Classification

Serum creatinine and cystatin C (gentian) were measured in fasting serum using a Beckman DxC automated chemistry analyzer. Primary analyses used GFR estimated using the CKD Epidemiology Collaboration (CKD-EPI) creatinine–cystatin C equation (2012)[17] to follow the precedent of the original eligibility criteria, categorizations, and analyses. The results were compared with a race-neutral CKD-EPI creatinine–cystatin C equation (2021).[18]

Oral Glucose Tolerance Test, Hyperinsulinemic–Euglycemic Insulin Clamp, and Intravenous Glucose Tolerance Test

A standard 75-g OGTT was performed approximately 1 week after a hyperinsulinemic–euglycemic insulin clamp and short intravenous glucose tolerance test (IVGTT). After collection of fasting plasma, IVGTT was performed with an infusion of 20% dextrose (11.4 g/m^2 over 60 seconds), and frequent plasma sampling (1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 22, 24, 27, and 30 minutes) was collected for 30 minutes. During OGTT, plasma glucose, insulin, total GLP-1, and total GIP concentrations were measured at −10, −5, 0, 30, 60, 90, and 120 minutes. We averaged -10 to 0 time points to generate baseline fasting values. Plasma glucagon levels were measured at 0, 30, and 120 minutes. Postprandial incretin hormone responses were calculated as area under the curve (AUC) using the trapezoidal rule for the total duration of OGTT and evaluated both as total AUC (tAUC) and incremental AUC (iAUC), the latter only measuring the area above the baseline level representing incretin response in the case of unequal fasting incretin levels. Glucose iAUC and 2-hour plasma glucose were calculated as a measure of glucose tolerance. Insulinogenic index was used to quantify the difference in plasma insulin divided by the difference in plasma glucose from baseline to 30 minutes of the OGTT. Acute incretin effect was calculated using insulin responses during OGTT and IVGTT: incretin effect (%)=$100\%\times(AUC_{OGTT}-AUC_{IVGTT})/AUC_{OGTT}$ as reported previously.[19] Clamp insulin sensitivity was used as the primary measure of insulin sensitivity. Details of the clamp, OGTT, and IVGTT procedures have been published previously.[20]

Laboratory Measures

Plasma samples were assayed for total GLP-1 and total GIP using multiplex electrochemiluminescence (Meso Scale Discovery, Rockville, MD). Plasma glucagon was measured by ELISA (Mercodia). DPP-4 antigen concentration was determined by ELISA (eBioscience). Blood glucose concentrations were measured using the glucose hexokinase method (Roche Module P Chemistry autoanalyzer; Roche, Basel, Switzerland), and blood insulin concentrations were measured using two-site immune-enzymometric assay (Tosoh 2000 Autoanalyzer). C-peptide concentrations were determined using a standard double-antibody RIA (Diagnostic Products Corporation, Los Angeles, CA). DPP-4 activity was assayed by incubating plasma with a colorimetric substrate, l-glycyl-l-prolyl p-nitroanilide, hydrochloride (Sigma), at 37°C. Inflammatory biomarkers were measured in fasting blood. C-reactive protein (CRP) was measured with a Beckman Coulter[21] DxC chemistry analyzer. Serum TNF-α, IL-6, IFN-γ, and IL-1β were performed using commercial multiplex electroluminescence assays (Meso Scale Discovery).

Covariates

Demographic characteristics and medical history of participants were self-reported. Cardiovascular disease was defined as a physician diagnosis of myocardial infarction, stroke, resuscitated cardiac arrest, or heart failure or a history of coronary or cerebral revascularization. The Human Activity Profile maximum activity score was used to quantify physical activity. Food intake was recorded using 3 days of prospective food diaries analyzed with Nutrition Data System for Research software. Body composition was measured by dual-energy X-ray absorptiometry (general electric Lunar or Prodigy and integrated dual-energy X-ray absorptiometry).

Statistical Analyses

Linear regression was used to test associations of CKD status with incretins (tAUC and iAUC), measures of insulin resistance, and inflammatory biomarkers adjusting biologically relevant confounders. Spearman correlation coefficient was used to evaluate the univariate relationship between kidney function and incretin levels during the OGTT. The rate of acute incretin peripheral response was calculated using the difference in plasma incretin levels at baseline and 30 minutes after OGTT and over time. $P < 0.05$ was considered significant for all analyses unless stated otherwise. Analyses were conducted using R version 4.2.2.[22] Box plots and scatterplots were made using GraphPad Prism version 10.0.0.

Study Approval

The study was approved by the University of Washington Human Subjects Division. All participants provided written informed consent.

Results

Characteristics of the Study Participants

The study included a total of 98 participants, among whom 59 had CKD and 39 were healthy controls. Participants with CKD had a mean (range) eGFR of 37.6 (9.5–59.5 ml/min per 1.73 m^2) and mean ($\pm$ SD) age of 63.6±13.9 years with a female prevalence of 51%, and 22% self-reported as being of Black race. Controls had a mean (range) eGFR of 88.8 (61–117 ml/min per 1.73 m^2) and mean age of 61±12.4 with a female prevalence of 44%, and 22% self-reported as being of Black race. Prevalence of impaired fasting glucose was 48% in controls and 59% among patients with CKD. Participant characteristics are listed in Table 1.

Fasting Incretin Levels and Incretin Response during an OGTT

In the overall cohort, eGFR was inversely correlated with only total GLP-1 levels (tAUC), but not GLP-1 iAUC (Figure 1, A and C). In comparison, eGFR was inversely correlated with both GIP tAUC and GIP iAUC in the overall cohort (Figure 1, B and D). CKD was associated with higher fasting GLP-1 levels with a mean of 16.2±11.6 compared with 8.5±3.3 pM among controls ($P < 0.01$) (Table 2 and Supplemental Table 1). GLP-1 tAUC measured during the OGTT was higher in participants with CKD versus controls (Figure 2A and Table 2). After adjustment CKD was associated with a 1100 pM×min higher GLP-1 tAUC (95% confidence intervals [CIs], 119 to 2080; $P = 0.03$) (Table 3). Sensitivity analysis further adjusting for impaired glucose tolerance (IGT) attenuated the association to an estimated mean difference of 934 pM×min higher GLP-1 tAUC (95% CI, −30 to 1899; $P = 0.06$). By contrast, we found no significant difference in GLP-1 iAUC compared with controls (Tables 2 and 3).

Fasting GIP level was higher in the CKD group with a mean of 134.5±104.1 versus 97±112.6 pg/ml in controls ($P < 0.01$) (Table 2 and Supplemental Table 1), but the estimated mean difference was NS after adjusting for potential confounders (Supplemental Table 1). By contrast, both GIP tAUC and iAUC were higher in patients with CKD compared with controls (Figure 2B and Table 2). Adjusting for potential confounders attenuated the estimated association by 24% to an estimated mean difference of 15,271 pg×min/ml higher GIP iAUC (95% CI, 387 to 30,154; $P = 0.04$) in patients with CKD compared with controls (Table 3). Sensitivity analysis further adjusting for IGT status did not attenuate the estimated association between CKD and GIP iAUC. After further adjusting for IGT, CKD was associated with a 17,641 pg×min/ml greater GIP iAUC (95% CI, 2763 to 3251; $P = 0.02$) compared with controls. These differences in incretin levels were observed in the absence of differences in fasting plasma DPP-4 antigen levels and DPP-4 activity among patients with CKD and controls (Figure 3, A and B).

The rate of acute GIP increase in the first 30 minutes of OGTT was greater in patients with CKD compared with controls. The mean rate of increase in GIP within the first 30 minutes of the OGTT was 249±111 versus 177±101 pg/ml per minute in patients with CKD and controls, respectively. Patients with CKD had an estimated mean 167 pg/ml per minute greater rate of increase in GIP (95% CI, 50 to 284; $P < 0.01$) compared with controls after adjustment for potential confounders (Supplemental Table 2). Further adjustment for fasting plasma GIP levels did not meaningfully affect estimates of association. By contrast, the patients with CKD did not differ in their mean rate of increase in GLP-1 (Supplemental Table 2).

Insulinotropic Effects of GLP-1 and GIP during OGTT

Patients with CKD on average had lower acute incretin insulinotropic effect with a mean (SD) of 60% (21%) among controls compared with 51% (21%) in patients with CKD ($P = 0.06$). After adjustment for potential confounders, CKD was associated with 14% lower incretin effect (95% CI, −25 to −2.5; $P = 0.02$). Total postprandial insulin levels during the OGTT did not significantly differ between patients with

Table 1. Characteristics of participants in the Study of Glucose and Insulin in Renal Disease

Characteristics	Controls	CKD
No.	39	59
Demographics		
Age, mean (SD)	61.0 (12.4)	63.6 (13.9)
Female, No. (%)	17 (44)	30 (51)
Race, No. (%)		
Asian/Pacific Islander	1 (3)	5 (8)
Black	4 (10)	13 (22)
White	34 (87)	41 (69)
Medical history and lifestyle, No. (%)		
History of CVD	2 (5)	19 (32)
Currently smoking	3 (8)	10 (17)
Physical activity, HAP score	83.5 (8.7)	76.8 (9.5)
Calorie intake, kcal/d	2047.9 (556.4)	1758.2 (540.8)
Fat intake, g/d	81.8 (32.1)	70.6 (26.4)
Carbohydrate intake, g/d	243.1 (78.3)	209.2 (79.0)
Protein intake, g/d	79.6 (24.5)	71.0 (26.1)
Medication use		
Any antihypertensive medication	13 (33)	53 (90)
RAS antagonists	8 (21)	38 (64)
Diuretics	2 (5)	27 (46)
β-blockers	3 (8)	23 (39)
Calcium-channel blockers	3 (8)	27 (46)
Physical characteristics, mean (SD)		
BMI (kg/m^2)	27.5 (6.3)	30.2 (6.0)
Body weight (kg)	82.1 (20.6)	88.1 (19.8)
Fat-free mass (kg)	56.1 (13.1)	53.7 (11.7)
Fat mass (kg)	27.1 (14.0)	31.9 (11.6)
Laboratory data		
Serum creatinine (mg/dl), median (IQR)	0.9 (0.7–1.0)	1.7 (1.5–2.1)
Serum cystatin C (mg/L), median (IQR)	0.9 (0.7–1.0)	1.6 (1.4–2.0)
eGFR (ml/min per 1.73 m^2), CKD-EPI 2012, mean (SD)	88.8 (17.1)	37.6 (12.5)
eGFR (ml/min per 1.73 m^2), CKD-EPI 2021, mean (SD)	91.1 (18.3)	38.4 (12.3)
Urine albumin excretion rate (mg/24 h), median (IQR)	5.7 (3.5–8.5)	39.2 (14.2–225.1)
CRP (mg/dl), median (IQR)	0.1 (0.06–0.3)	0.3 (0.1–0.7)
IL-6 (pg/ml), median (IQR)	0.9 (0.6–1.4)	1.5 (0.9–2.1)
TNF-α (pg/ml), median (IQR)	1.6 (1.3–1.9)	2.7 (2.1–3.0)

CKD was defined as eGFR <60 ml/min per 1.73 m^2; controls as ≥60 ml/min per 1.73 m^2. Data are means (SDs) for continuous variables, *N* (percentages) for categorical variables, and medians (interquartile ranges). CKD-EPI, CKD Epidemiology Collaboration; CRP, C-reactive protein; CVD, cardiovascular disease; HAP, Human Activity Profile; IQR, interquartile range; RAS, renin-angiotensin system.

CKD and controls, whereas C-peptide levels were more consistently greater at each time point in patients with CKD during the OGTT (Figure 2, C and D). No significant differences were observed in insulin response (insulin iAUC) and insulinogenic index between patients with CKD and controls (Table 2). Similarly, we found no meaningful difference by CKD status in glucose tolerance measured by glucose iAUC (Figure 2E and Table 2). The correlation of GLP-1 and GIP iAUCs with insulin, C-peptide, and glucose iAUCs were overall weaker in patients with CKD compared with controls (Supplemental Figure 1, A–F).

Plasma Glucagon Levels during OGTT

Fasting plasma glucagon levels were not significantly different between patients with CKD and controls (Figure 2F, Table 2, and Supplemental Table 1). Plasma glucagon levels were higher at 30 minutes and 120 minutes in patients with CKD compared with controls (Figure 2F and Table 2). The percent change in glucagon levels from baseline to 30 minutes after OGTT was attenuated in patients with CKD with a median (interquartile range [IQR]) of −27% [−11 to −46] versus −38% [−19 to −57] among controls. The percent change from baseline was also modestly attenuated at 2 hours after OGTT among patients with CKD with a median (IQR) of −70% (−57 to −80) compared with −78% (−60 to −88) in controls.

Association of Inflammation with Incretin Response

In the overall cohort, plasma TNF-α levels were significantly associated with GIP iAUC, and CRP levels were significantly associated with GLP-1 iAUC (Supplemental Table 3). In the CKD subgroup, greater CRP was also associated with greater GLP-1 response (Supplemental Table 3). Among patients with CKD, each 1 mg/dl greater plasma CRP was associated with 0.58 greater pM GLP-1 response (95% CI, 0.37 to 0.8; $P < 0.01$) in CKD (Supplemental Table 3).

Sensitivity Analyses Using the CKD-EPI Creatinine–Cystatin C 2021 Equation

The eGFR was similar among patients with CKD and controls compared with the 2012 equation (Table 1). The

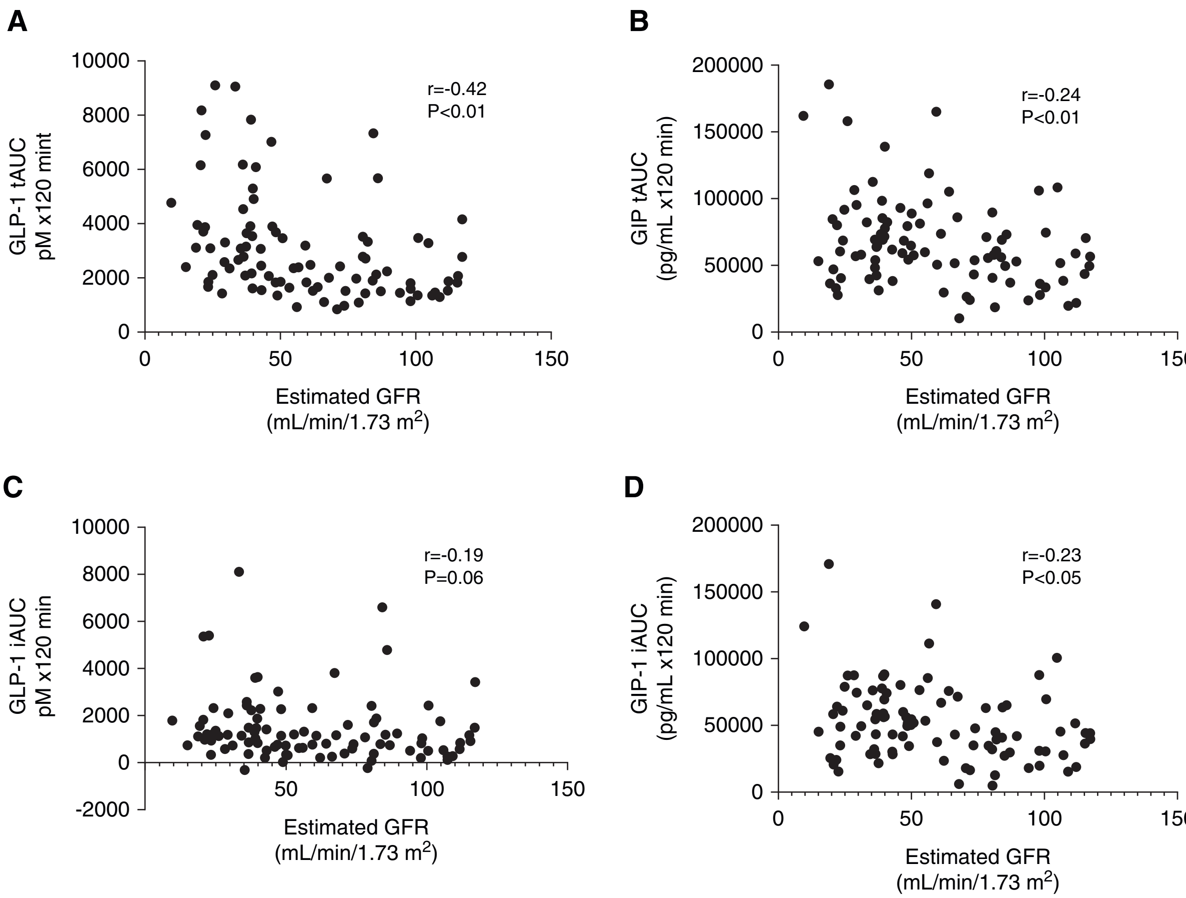

Figure 1. Association of estimated GFR with plasma incretin levels during OGTT. (A and B) Association of eGFR with GLP-1 and GIP tAUCs, respectively and (C and D) association of eGFR with GLP-1 and GIP iAUC, respectively. eGFR <30 (n=17), eGFR 30–45 (n=22), eGFR 45–60 (n=19), and eGFR >60 (n=39). CKD-EPI creatinine–cystatin C equation (2012) was used to estimate GFR. Spearman correlation coefficients were used to estimate the univariate relationship between incretin response and kidney function. CKD-EPI, CKD Epidemiology Collaboration; GIP, glucose-dependent insulinotropic polypeptide; iAUC, incremental area under the curve; OGTT, oral glucose tolerance testing; tAUC, total area under the curve.

results using the 2021 GFR equation were similar to those for the 2012 equation (Supplemental Figure 2 and Supplemental Table 4).

Discussion

Our findings demonstrate that the presence and severity of nondiabetic CKD are associated with greater plasma levels of incretins during fasting and in response to an OGTT. The higher incretin levels during fasting and postprandial conditions were observed in the absence of any significant difference in DPP-4 levels. Acute GIP release and GIP response (iAUC) during the OGTT were higher in patients with CKD versus controls. The correlation of incretin levels with OGTT-stimulated insulin or C-peptide was attenuated in those with CKD compared with controls. Concomitantly, CKD was associated with higher plasma glucagon levels and impaired glucagon suppression after OGTT. In CKD, inflammation was associated with higher incretin response. Overall, our findings show that nondiabetic moderate-to-severe CKD is associated with greater incretin levels and an augmented GIP response during OGTT do not translate into meaningful improvements in insulin, glucose, or glucagon homeostasis.

Higher fasting and postprandial plasma incretin levels in CKD were independent of differences in circulating fasting DPP-4 levels and activity, suggesting these differences are unlikely due to lower incretin degradation. The influence of the uremic milieu on potential alternative incretin degradation pathways is unknown; however, our findings are consistent with other studies in patients with nondiabetic ESKD. One prior study showed greater GLP-1 levels in response to a high-calorie mixed meal in nondiabetic patients with ESKD compared with healthy controls,[23] whereas another small study of nine nondiabetic patients on hemodialysis and ten healthy controls found higher fasting and postprandial total GIP response during a standardized meal.[24] Indeed, a greater incretin response is induced after ingestion of a mixed meal compared with oral glucose demonstrating the synergistic impact of other nutrients (fats and proteins) with glucose to promote GLP-1 and GIP secretion.[25,26] This contrasts with intravenous (IV) glucose administration where it does not stimulate incretin secretion.[25] Despite the use of OGTT in our study, we found stark differences in incretin levels and incretin response comparing patients with CKD with controls even after adjusting for confounding factors. We speculate that

Table 2. Fasting and oral glucose tolerance testing glucose homeostasis and physiological measurements by CKD status

Measurements	Controls (n=39)	CKD (n=59)	P Value
Fasting measurements, mean (SD)			
Fasting glucose, mg/dl	98.4 (9.2)	100.7 (8.6)	0.19
Fasting glucagon, pmol/L	5.7 (3.7)	6.8 (4.5)	0.20
Fasting insulin, μU/ml	6.9 (4.6)	10.3 (7.0)	<0.01
GLP-1, pM	8.5 (3.3)	16.2 (11.6)	<0.01
GIP, pg/ml	96.9 (112.6)	134.5 (104.1)	<0.01
C-peptide, ng/ml	2.1 (1.0)	3.8 (1.8)	<0.01
Free fatty acid, mEq/L	0.5 (0.1)	0.5 (0.2)	0.73
OGTT measurements, mean (SD)			
Insulinogenic index, μU/ml/mg/dl	1.0 (1.2)	1.1 (0.9)	0.64
Glucose tAUC, mg×120 min/ml	19,220 (3705)	19,712 (3189)	0.48
Glucose iAUC, mg×120 min/ml	7402 (3127)	7583 (2884)	0.55
2-h glucose, mg/dl	149.1 (44.5)	151.6 (35.4)	0.75
Insulin iAUC, 120 min×μU/ml	6108 (4748)	7975 (5405)	0.08
30 min glucagon, pmol/L	3.5 (2.0)	5.1 (3.6)	0.01
2-h glucagon, pmol/L	1.3 (0.9)	2.2 (1.7)	<0.01
2-h GLP-1, pM	14.8 (11.6)	20 (11.7)	0.04
2-h GIP, pg/ml	442 (313)	622 (365)	0.01
GLP-1 iAUC, pM×120 min	1364 (1484)	1531 (1452)	0.58
GLP-1 tAUC, pM×120 min	2384 (1546)	3486 (1996)	<0.01
GIP iAUC, pg/ml×120 min	42,365 (25,061)	62,370 (33,453)	<0.01
GIP tAUC, pg/ml×120 min	53,994 (28,191)	78,510 (38,924)	<0.01
2-h C-peptide, ng/ml	10.1 (4.0)	15.7 (7.8)	<0.01
C-peptide iAUC, ng/ml×120 min	724 (329)	913 (443)	<0.01
2-h free fatty acid, mEq/L	0.04 (0.04)	0.07 (0.06)	<0.01
Hyperinsulinemic–euglycemic clamp			
Insulin sensitivity, mg/min/μU/ml	5.0 (2.0)	3.9 (2.0)	0.03
2-h GLP-1, pM	4.2 (1.7)	10.3 (9.1)	<0.01
2-h GIP, pg/ml	65.9 (50.2)	98.9 (82.8)	0.01
2-h glucagon, pmol/L	1.6 (1.6)	2.4 (2.6)	0.13

Cells represent means (SDs). GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; iAUC, incremental area under the curve; OGTT, oral glucose tolerance testing; tAUC, total area under the curve.

using a mixed meal test to assess incretin response in our study would have allowed us to detect a greater difference among patients with CKD and controls. Indeed, future studies with a standardized mixed meal should confirm our findings and investigate whether CKD modifies in nutrient-stimulated incretin responses.

In our study, CKD was associated with a greater rate of GIP increase in the first 30 minutes of OGTT compared with that in controls (Supplemental Table 2) independent of differences in fasting levels of GIP, implying these differences may be independent of lower clearance of GIP. Controversy exists regarding the role of kidney clearance on incretin response. A prior small case–control study in a select group of patients with more modest kidney disease (mean creatinine clearance 46 ml/min) suggested similar metabolic clearance rates and plasma $t_{1/2}$ of intact GLP-1 and intact GIP but prolonged metabolite half-lives with IV GLP-1 and GIP infusion in patients with CKD compared with controls.[27] Two studies examining postprandial incretin response in patients with ESKD treated with dialysis have suggested a preserved ability to degrade and eliminate GLP-1 and GIP compared with controls.[19,23] Using GLP-1 and GIP infusions, the same group reported a preserved but lower degradation and elimination of intact metabolites of GLP-1 and GIP in patients with dialysis-dependent ESKD.[28] Whether exogenous (nonphysiological) incretin infusions have a different pharmacokinetics and degradation pattern compared with endogenous secretion of GLP-1 and GIP from enterocytes needs to be investigated. Our study is the first demonstrating unaltered DPP-4 levels and activities in nondiabetic CKD supporting these prior observations in ESKD.

Disruption of postprandial incretin hormone response (iAUC) in CKD seemed to coincide with blunted regulatory impact of incretins on insulin, C-peptide, and glucagon homeostasis during the OGTT. In healthy adults, GIP is considered more strongly insulinotropic than GLP-1.[29] Consistent with these findings, we found a stronger positive correlation between GIP response and insulin/C-peptide compared with GLP-1. Furthermore, CKD was associated with a weaker correlation between GIP response and insulin/C-peptide compared with controls. This is in line with our findings showing a lower acute insulinotropic incretin effect in patients with CKD compared with healthy controls. In comparison, we found no meaningful correlation of GLP-1 with insulinotropic response. Our findings expand on prior studies suggesting nondiabetic patients with CKD demonstrate a blunted insulinotropic effect of incretins akin to patients with type 2 diabetes and normal kidney function.[30,31] However, patients with CKD appeared to have numerically greater baseline-corrected insulin response (insulin iAUC) reflecting lower insulin clearance[3] and a similar acute insulin response estimated by the insulinogenic index compared with controls (Table 2). This may suggest altered glucose homeostasis in patients

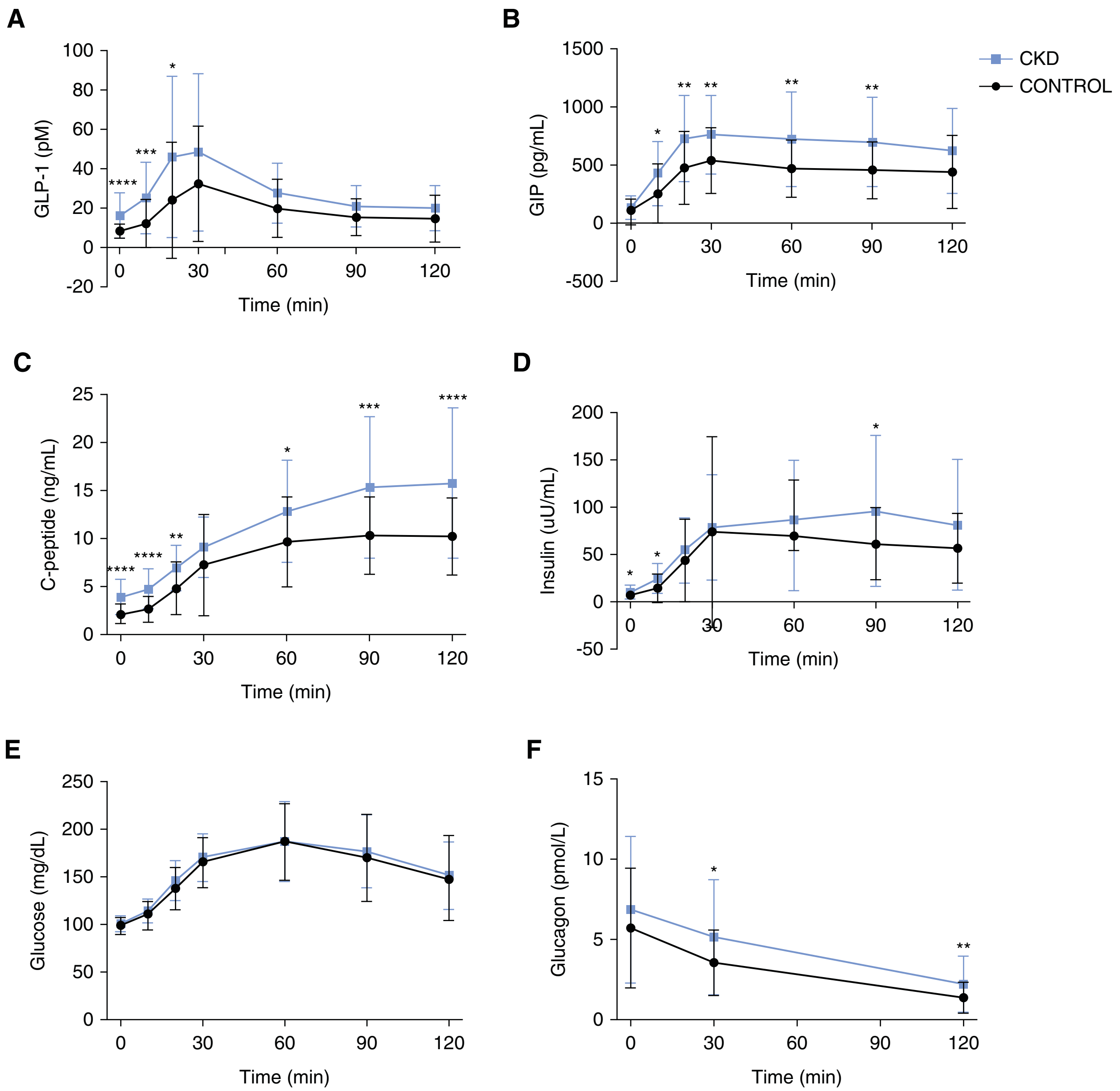

Figure 2. Changes in plasma glucose, glucagon, and proinsulin factors in response to OGTT comparing patients with CKD and controls. Figure represents plasma level changes of (A) GLP-1, (B) GIP, (C) C-peptide, (D) Insulin, (E) glucose, and (F) glucagon over time. Data points and error bars are means and SD, respectively. Unpaired *t* test corrected by multiple hypothesis testing (Bonferroni) was used to evaluate differences between patients with CKD and controls at each time point. ****$P < 0.0001$, ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

with CKD may be attributed to inadequate augmentation of the insulin response by incretin hormones (especially GLP-1) or resistance to insulin's actions on peripheral tissues. Our findings are consistent with results from a randomized double-blind study that also showed nondiabetic patients with ESKD exhibit lower incretin-stimulated insulin secretion despite adequate insulin response during IV glucose stimulation.[32] Mechanistic studies of CKD in 5/6th nephrectomized mice showed impaired β-cell insulin secretion in response to glucose,[33] but none have investigated β-cell resistance to GIP-induced insulin secretion. Thus, it is important to evaluate the incretin response to carbohydrate consumption in nondiabetic CKD, especially in the β cells of the endocrine pancreas where GLP-1 and GIP receptors are abundantly expressed.[34]

The attenuated suppression of glucagon during the OGTT in nondiabetic moderate-to-severe CKD suggests potential disruption of α-cell response to incretins in CKD. Despite declines in glucagon levels during the OGTT in both patients with CKD and controls, postprandial glucagon levels remained significantly higher in the CKD group compared with controls. These findings are in line with other studies of patients with type 2 diabetes and nondiabetic patients with ESKD.[5,19,35–37] It suggests that an altered counter-regulatory balance between GIP induction and GLP-1 suppression of glucagon may contribute to an

Table 3. Association of CKD with measures of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide during 2-hour oral glucose tolerance testing

Covariate Adjustment	GLP-1 AUC				GIP AUC			
	GLP-1 iAUC		GLP-1 tAUC		GIP iAUC		GIP tAUC	
	Difference (95% CI), pM×min	*P* Value	Difference (95% CI), pM×min	*P* Value	Difference (95% CI), (pg×min)/ml	*P* Value	Difference (95% CI), (pg×min)/ml	*P* Value
None (unadjusted)	166 (−435 to 769)	0.58	1102 (350 to 1854)	<0.01	20,005 (7517 to 32,493)	<0.01	24,516 (10,116 to 38,916)	<0.01
Age, sex, and race	92 (−504 to 690)	0.76	1192 (406 to 1978)	<0.01	18,971 (5923 to 32,018)	<0.01	21,613 (6885 to 36,340)	<0.01
Weight	162 (−447 to 771)	0.60	1224 (417 to 2031)	<0.01	19,629 (6244 to 33,014)	<0.01	21,908 (6783 to 37,032)	<0.01
Fat mass	216 (−401 to 833)	0.49	1223 (400 to 2045)	<0.01	19,715 (5800 to 33,630)	<0.01	21,349 (5670 to 37,029)	<0.01
Fat-free mass	144 (−515 to 803)	0.66	1095 (217 to 1972)	0.01	21,408 (6540 to 36,277)	<0.01	23,465 (6720 to 40,210)	<0.01
Physical activity	96 (−570 to 761)	0.77	1019 (135 to 1903)	0.02	19,725 (4849 to 34,600)	<0.01	21,558 (4809 to 38,308)	0.01
Calorie intake	93 (−628 to 814)	0.79	1022 (62 to 1981)	0.04	14,485 (−2.7 to 28,972)	0.05	15,510 (−583 to 31,603)	0.06
Smoking status	92 (−634 to 818)	0.80	1018 (53 to 1983)	0.04	14,490 (−100 to 29,080)	0.05	15,528 (−677 to 31,733)	0.06
Fully adjusted model	122 (−619 to 864)	0.74	1100 (119 to 2080)	0.03	15,271 (387 to 30,154)	0.04	16,974 (515 to 33,432)	0.04

Mean differences represent the differences associated with CKD (versus controls) with 95% confidence intervals and *P* values. Covariates were added one at a time to the base model that included age, sex, and race. The fully adjusted model is adjusted for age, sex, race, fat-free mass, fat mass, physical activity, calorie intake, smoking status, and cardiovascular disease. Glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide were measured during oral glucose tolerance testing. CI, confidence interval; CVD, cardiovascular disease; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; iAUC, incremental area under the curve; tAUC, total area under the curve.

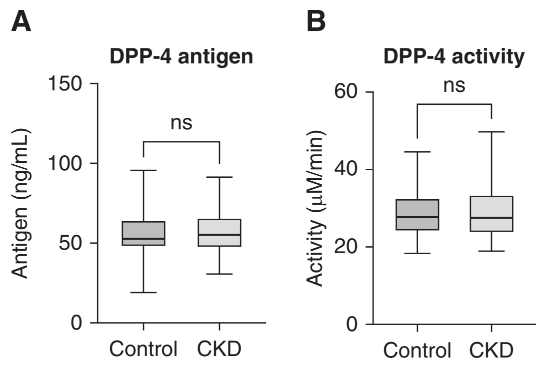

Figure 3. Comparison of fasting plasma DPP-4 antigen and activity levels among patients with CKD (*n*=43) and controls (*n*=34). (A) DPP-4 antigen levels and (B) DPP-4 activity levels. Box plots represent median and IQR, and the whiskers represent minimum and maximum values. Unpaired *t* test was used to determine the difference between the two groups. DPP-4, dipeptidyl peptidase-4; IQR, interquartile range.

impaired glucagon homeostasis in CKD during OGTT-induced hyperglycemia. Sustained and elevated postprandial glucagon levels could have adverse impacts on glycemic control and amino acid catabolism contributing to muscle wasting in patients with CKD.[38–40]

Inflammation may contribute to heightened incretin response to an OGTT. The association of inflammatory biomarkers, including CRP and IL-6, with GLP-1 levels has been reported in other observational studies.[41–43] Interestingly, the contrary has been observed with long-term incretin-based therapies, significantly decreasing circulating proinflammatory cytokines.[44–46] Mechanistic studies are needed to investigate the link between systemic inflammation and incretin levels in CKD and whether lifestyle or pharmacologic therapies reducing inflammation and catabolism simultaneously improve incretin effects.

Our study had notable strengths. First, we recruited a well-characterized group of nondiabetic participants with CKD across the spectrum of moderate-to-severe CKD, including measures of body composition and lifestyle factors. Second, we used an OGTT to comprehensively measure gut-derived incretin hormones, glucagon, insulin, and glucose. Third, we used a rigorous analysis method adjusting for a wide range of clinically relevant confounders. However, our study was not without limitations. First, our assays measured total GLP-1 and GIP levels in plasma, so the proportion of activity from the total GLP-1 and GIP was not directly measured. Second, sample collections during OGTT were acquired without the addition of a DPP-4 inhibitor which may have affected the levels of glucagon, GLP-1, and GIP. Despite similar DPP-4 expression and activity and standardized sample collection, degradation of incretin hormones may not have stopped at sampling. Third, the incretin effect estimate reported by comparing OGTT and IVGTT insulin response was only limited to the first 30 minutes of glucose ingestion/infusion. Finally, both controls and patients with CKD included individuals with IGT. However, the inclusion of individuals with IGT in our control group may suggest that observed estimated differences in incretin levels and responses between patients with CKD and controls are conservative.

In conclusion, nondiabetic CKD is associated with disruption of incretin homeostasis and evidence of attenuated physiological/regulatory impact of incretins on insulin, C-peptide, and glucagon secretion. These changes may contribute to the metabolic dysregulation associated with kidney disease and reveal a potential role for incretin mimetics to counter attenuated incretin effects. Indeed, a recent pharmacokinetic study of a combination of GLP-1 and GIP in the form of single-dose tirzepatide, a dual GLP-1 and GIP receptor agonist, showed similar drug clearance and tolerability in healthy controls compared with patients across all stages of CKD, including ESKD.[47] Studies are needed to investigate the differential efficacy of GLP-1 and GIP single and dual agonists on insulin, glucose, and glucagon homeostasis and links to outcomes in nondiabetic CKD.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/CJN/C58.

Funding

I.H. de Boer: NIDDK (R01DK087726 and K01 DK102851) and National Institute of Diabetes and Digestive and Kidney Diseases (R01DK129793), B. Roshanravan: Dialysis Clinics (C-4122). B.P. Cummings: National Institute of Diabetes and Digestive and Kidney Diseases (R56DK124853). J. Gamboa: NIDDK (R01DK125794). A. Ahmadi: NIDDK (U2CDK133488). This work was supported by NIDDK (R01DK125794), Diabetes Research Center, University of Washington (P30 DK017047), and Northwest Kidney Centers.

Acknowledgments

We thank Anthony Dematteo at Vanderbilt University who measured plasma DPP-4 antigen and activity levels. We would like to express our sincere gratitude to Steven Kahn for his valuable feedback and insightful comments on this manuscript. We thank all the participants in the Study of Glucose and Insulin in Renal Disease cohort for their contributions to this investigation.

Because Baback Roshanravan is an editor for the *CJASN*, he was not involved in the peer-review process for this manuscript. Another editor oversaw the peer-review and decision-making process for this manuscript.

Author Contributions

Conceptualization: Armin Ahmadi, Bethany P. Cummings, Ian H. de Boer, Jorge Gamboa, Baback Roshanravan.

Data curation: Armin Ahmadi, Sili Fan, Madelynn Tucker, Leila R Zelnick.

Formal analysis: Armin Ahmadi, Sili Fan.

Funding acquisition: Bethany P. Cummings, Ian H. de Boer, Baback Roshanravan.

Investigation: Bethany P. Cummings, Ian H. de Boer, Jorge Gamboa, Baback Roshanravan.

Methodology: Armin Ahmadi, Bethany P. Cummings, Sili Fan, Jorge Gamboa, Talat Alp Ikizler, Baback Roshanravan.

Project administration: Bethany P. Cummings, Ian H. de Boer, Baback Roshanravan.

Resources: Bethany P. Cummings, Ian H. de Boer, Jorge Gamboa, Baback Roshanravan.

Supervision: Bethany P. Cummings, Ian H. de Boer, Baback Roshanravan.

Visualization: Armin Ahmadi, Sili Fan.

Writing – original draft: Armin Ahmadi, Jorge Gamboa, Baback Roshanravan.

Writing – review & editing: Armin Ahmadi, Brian J. Bennett, Lars F. Berglund, Bethany P. Cummings, Ian H. de Boer, Bamba Enkhmaa, Jorge Gamboa, Talat Alp Ikizler, Jennifer E. Norman, Baback Roshanravan, Madelynn Tucker, Leila R. Zelnick.

Data Sharing Statement

A complete deidentified patient metadata supporting the findings in this study has been made available on Figshare (DOI: https://doi.org/10.6084/m9.figshare.24978102.v1). Additional dietary information will be made available to share upon request. Summary statistics are described in the Methods section of the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/C57.

Supplemental Table 1. Association of CKD with fasting GLP-1, GIP, and glucagon measurements.

Supplemental Table 2. Estimated differences in the rate of acute incretin peripheral response between patients with CKD and controls.

Supplemental Table 3. Association of inflammatory biomarkers with incretin response during OGTT in patients with CKD and controls.

Supplemental Table 4. Association of CKD with measures of GLP-1 and GIP response during 2-hour OGTT using the CKD-EPI creatinine–cystatin C equation (2021).

Supplemental Figure 1. Correlation between incretin response with insulin, C-peptide, and glucose iAUCs in patients with CKD and controls during OGTT.

Supplemental Figure 2. Comparison of fasting plasma DPP-4 antigen and activity levels among patients with CKD (n=41) and controls (n=36) using the CKD-EPI creatinine–cystatin C equation (2021).

References

1. Slee AD. Exploring metabolic dysfunction in chronic kidney disease. *Nutr Metab (Lond).* 2012;9(1):36. doi:10.1186/1743-7075-9-36
2. RahhalM-N, Gharaibeh NE, Rahimi L, Ismail-Beigi F. Disturbances in insulin–glucose metabolism in patients with advanced renal disease with and without diabetes. *J Clin Endocrinol Metab.* 2019;104(11):4949–4966. doi:10.1210/jc.2019-00286
3. de Boer IH, Zelnick L, Afkarian M, et al. Impaired glucose and insulin homeostasis in moderate-severe CKD. *J Am Soc Nephrol.* 2016;27(9):2861–2871. doi:10.1681/ASN.2015070756
4. Rapa SF, Di Iorio BR, Campiglia P, Heidland A, Marzocco S. Inflammation and oxidative stress in chronic kidney disease-potential therapeutic role of minerals, vitamins and plant-derived metabolites. *Int J Mol Sci.* 2019;21(1):263. doi:10.3390/ijms21010263
5. Liu JJ, Liu S, Gurung RL, et al. Relationship between fasting plasma glucagon level and renal function-A cross-sectional study in individuals with type 2 diabetes. *J Endocr Soc.* 2019;3(1):273–283. doi:10.1210/js.2018-00321
6. Ndumele CE, Neeland IJ, Tuttle KR, et al. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. *Circulation.* 2023;148(20):1636–1664. doi:10.1161/cir.0000000000001186
7. Gisterå A, Hansson GK. The immunology of atherosclerosis. *Nat Rev Nephrol.* 2017;13(6):368–380. doi:10.1038/nrneph.2017.51
8. Thomas SS, Dong Y, Zhang L, Mitch WE. Signal regulatory protein-α interacts with the insulin receptor contributing to muscle wasting in chronic kidney disease. *Kidney Int.* 2013;84(2):308–316. doi:10.1038/ki.2013.97
9. Nauck MA, Meier JJ. Incretin hormones: their role in health and disease. *Diabetes Obes Metab.* 2018;20(S1):5–21. doi:10.1111/dom.13129
10. Inagaki N, Seino Y, Takeda J, et al. Gastric inhibitory polypeptide: structure and chromosomal localization of the human gene. *Mol Endocrinol.* 1989;3(6):1014–1021. doi:10.1210/mend-3-6-1014
11. Bell GI, Santerre RF, Mullenbach GT. Hamster preproglucagon contains the sequence of glucagon and two related peptides. *Nature.* 1983;302(5910):716–718. doi:10.1038/302716a0
12. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects*. *J Clin Invest.* 1967;46(12):1954–1962. doi:10.1172/jci105685
13. Orskov C, Holst JJ, Nielsen OV. Effect of truncated glucagon-like peptide-1 [proglucagon-(78-107) amide] on endocrine secretion from pig pancreas, antrum, and nonantral stomach. *Endocrinology.* 1988;123(4):2009–2013. doi:10.1210/endo-123-4-2009
14. Pederson RA, Brown JC. Interaction of gastric inhibitory polypeptide, glucose, and arginine on insulin and glucagon secretion from the perfused rat pancreas. *Endocrinology.* 1978;103(2):610–615. doi:10.1210/endo-103-2-610
15. Giugliano D, Sportiello L, Capuano A, Maiorino M, Rossi F, Esposito K. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapy–focus on alogliptin. *Drug Des Devel Ther.* 2013;7:989–1001. doi:10.2147/dddt.S37647
16. Ahmad I, Zelnick LR, Robinson NR, et al. Chronic kidney disease and obesity bias surrogate estimates of insulin sensitivity compared with the hyperinsulinemic euglycemic clamp. *Am J Physiol Endocrinol Metab.* 2017;312(3):E175–E182. doi:10.1152/ajpendo.00394.2016
17. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012;367(1):20–29. doi:10.1056/NEJMoa1114248
18. Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis.* 2022;79(2):268–288.e1. doi:10.1053/j.ajkd.2021.08.003
19. Idorn T, Knop FK, Jørgensen M, Holst JJ, Hornum M, Feldt-Rasmussen B. Gastrointestinal factors contribute to glucometabolic disturbances in nondiabetic patients with end-stage renal disease. *Kidney Int.* 2013;83(5):915–923. doi:10.1038/ki.2012.460
20. Ahmadi A, Huda MN, Bennett BJ, et al. Chronic kidney disease is associated with attenuated plasma metabolome response to oral glucose tolerance testing. *J Renal Nutr.* 2023;33(2):316–325. doi:10.1053/j.jrn.2022.09.013
21. Ho JE, Larson MG, Vasan RS, et al. Metabolite profiles during oral glucose challenge. *Diabetes.* 2013;62(8):2689–2698. doi:10.2337/db12-0754
22. R Foundation for Statistical Computing. *R: A Language and Environment for Statistical Computing*; 2010.
23. Idorn T, Knop FK, Jørgensen M, Holst JJ, Hornum M, Feldt-Rasmussen B. Postprandial responses of incretin and pancreatic hormones in non-diabetic patients with end-stage renal disease. *Nephrol Dial Transplant.* 2013;29(1):119–127. doi:10.1093/ndt/gft353
24. Miyamoto T, Rashid Qureshi A, Yamamoto T, et al. Postprandial metabolic response to a fat- and carbohydrate-rich meal in patients with chronic kidney disease. *Nephrol Dial Transplant.* 2010;26(7):2231–2237. doi:10.1093/ndt/gfq697
25. Herrmann C, Göke R, Richter G, Fehmann HC, Arnold R, Göke B. Glucagon-like peptide-1 and glucose-dependent insulin-releasing polypeptide plasma levels in response to nutrients. *Digestion.* 2009;56(2):117–126. doi:10.1159/000201231

26. Koopman ADM, Rutters F, Rauh SP, et al. Incretin responses to oral glucose and mixed meal tests and changes in fasting glucose levels during 7 years of follow-up: the Hoorn Meal Study. *PLoS One*. 2018;13(1):e0191114. doi:10.1371/journal.pone.0191114
27. Meier JJ, Nauck MA, Kranz D, et al. Secretion, degradation, and elimination of glucagon-like peptide 1 and gastric inhibitory polypeptide in patients with chronic renal insufficiency and healthy control subjects. *Diabetes*. 2004;53(3):654–662. doi:10.2337/diabetes.53.3.654
28. Idorn T, Knop FK, Jørgensen MB, et al. Elimination and degradation of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with end-stage renal disease. *J Clin Endocrinol Metab*. 2014;99(7):2457–2466. doi:10.1210/jc.2013-3809
29. Gasbjerg LS, Bergmann NC, Stensen S, et al. Evaluation of the incretin effect in humans using GIP and GLP-1 receptor antagonists. *Peptides*. 2020;125:170183. doi:10.1016/j.peptides.2019.170183
30. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsbøll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96(3):737–745. doi:10.1210/jc.2010-2435
31. Knop FK, Vilsbøll T, Højberg PV, et al. Reduced incretin effect in type 2 diabetes: cause or consequence of the diabetic state? *Diabetes*. 2007;56(8):1951–1959. doi:10.2337/db07-0100
32. Jørgensen MB, Idorn T, Rydahl C, et al. Effect of the incretin hormones on the endocrine pancreas in end-stage renal disease. *J Clin Endocrinol Metab*. 2020;105(3):e564–e574. doi:10.1210/clinem/dgz048
33. Koppe L, Nyam E, Vivot K, et al. Urea impairs β cell glycolysis and insulin secretion in chronic kidney disease. *J Clin Invest*. 2016;126(9):3598–3612. doi:10.1172/jci86181
34. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: a pathophysiological update. *Diabetes Obes Metab*. 2021;23(S3):5–29. doi:10.1111/dom.14496
35. Butler PC, Rizza RA. Contribution to postprandial hyperglycemia and effect on initial splanchnic glucose clearance of hepatic glucose cycling in glucose-intolerant or NIDDM patients. *Diabetes*. 1991;40(1):73–81. doi:10.2337/diab.40.1.73
36. Knop FK, Vilsbøll T, Madsbad S, Holst JJ, Krarup T. Inappropriate suppression of glucagon during OGTT but not during isoglycaemic i.v. glucose infusion contributes to the reduced incretin effect in type 2 diabetes mellitus. *Diabetologia*. 2007;50(4):797–805. doi:10.1007/s00125-006-0566-z
37. Bilbrey GL, Faloona GR, White MG, Knochel JP, Borroto J. Hyperglucagonemia of renal failure. *J Clin Invest*. 1974;53(3):841–847. doi:10.1172/jci107624
38. Thiessen SE, Gunst J, Van den Berghe G. Role of glucagon in protein catabolism. *Curr Opin Crit Care*. 2018;24(4):228–234. doi:10.1097/mcc.0000000000000509
39. Hædersdal S, Lund A, Knop FK, Vilsbøll T. The role of glucagon in the pathophysiology and treatment of type 2 diabetes. *Mayo Clinic Proc*. 2018;93(2):217–239. doi:10.1016/j.mayocp.2017.12.003
40. Capozzi ME, DiMarchi RD, Tschöp MH, Finan B, Campbell JE. Targeting the incretin/glucagon system with triagonists to treat diabetes. *Endocr Rev*. 2018;39(5):719–738. doi:10.1210/er.2018-00117
41. Kahles F, Meyer C, Möllmann J, et al. GLP-1 secretion is increased by inflammatory stimuli in an IL-6–dependent manner, leading to hyperinsulinemia and blood glucose lowering. *Diabetes*. 2014;63(10):3221–3229. doi:10.2337/db14-0100
42. Ellingsgaard H, Hauselmann I, Schuler B, et al. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. *Nat Med*. 2011;17(11):1481–1489. doi:10.1038/nm.2513
43. Lebherz C, Kahles F, Piotrowski K, et al. Interleukin-6 predicts inflammation-induced increase of Glucagon-like peptide-1 in humans in response to cardiac surgery with association to parameters of glucose metabolism. *Cardiovasc Diabetol*. 2016;15(1):21. doi:10.1186/s12933-016-0330-8
44. Hogan AE, Gaoatswe G, Lynch L, et al. Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. *Diabetologia*. 2014;57(4):781–784. doi:10.1007/s00125-013-3145-0
45. Chaudhuri A, Ghanim H, Vora M, et al. Exenatide exerts a potent antiinflammatory effect. *J Clin Endocrinol Metab*. 2012;97(1):198–207. doi:10.1210/jc.2011-1508
46. Derosa G, Franzetti IG, Querci F, et al. Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-controlled trial. *Pharmacotherapy*. 2013;33(8):817–826. doi:10.1002/phar.1301
47. Urva S, Quinlan T, Landry J, Martin J, Loghin C. Effects of renal impairment on the pharmacokinetics of the dual GIP and GLP-1 receptor agonist tirzepatide. *Clin Pharmacokinet*. 2021;60(8):1049–1059. doi:10.1007/s40262-021-01012-2

AFFILIATIONS

[1]Division of Nephrology, Department of Internal Medicine, University of California, Davis, California
[2]Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee
[3]Division of Cardiovascular Medicine, Department of Internal Medicine, University of California, Davis, California
[4]Division of Endocrinology, Department of Internal Medicine, University of California, Davis, California
[5]Department of Surgery, Center for Alimentary and Metabolic Sciences, School of Medicine, University of California Davis, Sacramento, California
[6]Obesity and Metabolism Research Unit, Western Human Nutrition Research Center, USDA ARS, Davis, California
[7]Division of Nephrology and Kidney Research Institute, University of Washington, Seattle, Washington
[8]Division of Biostatistics, Department of Public Health Sciences, University of California, Davis, California
[9]Department of Internal Medicine, University of California, Davis, California
[10]Department of Medicine, Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, Tennessee
[11]Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, California