

Peripheral Insulin Resistance Is Associated with Copeptin in Patients with Chronic Kidney Disease

Juan Pablo Arroyo ^{1,2}, Elvis A. Akwo,¹ Andrew S. Terker,^{1,2} Aseel Alsouqi ¹, Gautam Bhavs,^{1,2} Raymond C. Harris,^{1,2,3} Adriana M. Hung, ^{1,2,3} and T. Alp Ikizler, ^{1,2,3}

Key Points

- We found that elevated levels of copeptin are associated with peripheral insulin resistance in nondiabetic patients with CKD stage 3–4.
- We found no correlation between copeptin levels and hepatic insulin resistance in patients with CKD stage 3–4 or in our control group.
- Further research is warranted to establish potential mechanistic links between vasopressin and peripheral insulin resistance in CKD.

Abstract

Background Insulin resistance is associated with cardiovascular disease risk and worsened kidney function. Patients with CKD have higher levels of insulin resistance. Elevated levels of copeptin (a surrogate for vasopressin levels) have been associated with an increased incidence and progression of CKD, and with incident diabetes mellitus. The purpose of our study was to examine the relationship between insulin resistance, copeptin, and CKD.

Methods We performed a cross-sectional study to investigate if insulin resistance was associated with higher copeptin levels in nondiabetic patients with stage 3–4 CKD versus controls. We measured plasma copeptin levels and used data from 52 patients with stage 3–4 CKD and 85 controls (eGFR ≥ 60 ml/min per 1.73 m²) enrolled in the Insulin Resistance in Chronic Kidney Disease (IRCKD) study. We then used a multivariable linear-regression model to assess the independent relationship between peripheral or hepatic insulin resistance and copeptin across levels of eGFR.

Results We found that in patients with CKD (eGFR of 30–60 ml/min per 1.73 m²), but not in controls, peripheral insulin resistance was significantly correlated with higher levels of log copeptin ($r = -0.21$, $P = 0.04$). In patients with CKD, when adjusted for age, sex, BMI, serum osmolality, log IL6, and log leptin/adiponectin ratio, each 1 SD decrease in insulin sensitivity was associated with a 39% increase in serum copeptin levels. The relationship between hepatic insulin resistance, copeptin, and eGFR is similar between controls and patients with reduced eGFR.

Conclusion Peripheral insulin resistance is associated with elevated copeptin levels in nondiabetic patients with stage 3–4 CKD. Further research into how the interaction between peripheral insulin resistance and elevated vasopressin affects CKD progression could be of interest.

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Introduction

Patients with CKD have more insulin resistance (IR) than what is observed in matched individuals without kidney disease (1). Prior data suggests that IR can hasten the development of kidney disease (2). Moreover, IR is associated with cardiovascular disease risk, and this relationship is magnified in patients with CKD (3). Therefore, mechanistic insights into how IR and CKD interact could have far-reaching

implications and aid in the development of novel therapeutic strategies.

The etiology of IR seen in patients with CKD is believed to be multifactorial and includes genetic variants, physical inactivity, inflammation, oxidative stress, and adipokine derangements. IR in CKD is driven primarily by defective glucose uptake in fat and skeletal muscle, but the identification of discrete, modifiable signaling pathways has remained elusive

¹Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

²Vanderbilt Center for Kidney Disease, Vanderbilt University School of Medicine, Nashville, Tennessee

³Department of Veterans Affairs, Nashville, Tennessee

Correspondence: Dr. T. Alp Ikizler, Division of Nephrology and Hypertension, Vanderbilt University Medical Center, S-3223 Medical Center North, 1161 21st Ave. South, Nashville, TN 37232-2372, or Dr. Adriana M. Hung, Tennessee Valley Healthcare System, Nashville VA Division of Nephrology and Hypertension Vanderbilt University Medical Center, Nashville, TN 37212. Email: alp.ikizler@vanderbilt.edu or Adriana.hung@vumc.org

(1,4). Vasopressin is the nine amino acid peptide hormone end product of a highly processed 164 amino acid prepropeptide. Vasopressin levels are elevated in patients with CKD, however, the mechanisms that lead to elevated vasopressin levels remain incompletely explained (5). High vasopressin levels have been associated with both increased incidence and progression of CKD from various etiologies (6–8). Elevated levels of copeptin (the carboxy-terminal product of the vasopressin precursor protein, a surrogate for vasopressin levels) correlate with albuminuria and incident diabetes mellitus (6,9–11). In healthy subjects, the infusion of vasopressin increased plasma glucose and glucose infusion led to decreased vasopressin levels within minutes, despite increased serum osmolality (10–12). More recently, vasopressin has been implicated in the development of fructose-induced metabolic syndrome (13). Together, these data suggest that vasopressin plays a key role in glucose-insulin homeostasis. In spite of the extensive data on the link between vasopressin and glucose homeostasis, whether IR is associated to elevated levels of vasopressin in patients with CKD has never been studied. We hypothesized that patients with CKD and IR would have higher copeptin levels than either patients with CKD and no IR or patients with IR and no CKD. Therefore, we performed a cross-sectional study to investigate if IR was associated with higher levels of copeptin levels in nondiabetic patients with stage 3–4 CKD versus controls.

Materials and Methods

Design and Study Sample

We conducted a cross-sectional study using data from 52 patients with CKD stages 3–4 and 85 controls (eGFR of ≥ 60 ml/min per 1.73 m^2) enrolled in the Insulin Resistance in Chronic Kidney Disease (IRCKD) study. Study participants were recruited from the Nashville US Department of Veterans Affairs (VA) Medical Center and Vanderbilt University Medical Center (VUMC) outpatient clinics. All study participants were nondiabetic and had a body mass index (BMI) $> 18 \text{ kg/m}^2$ at enrollment. Diabetes was ascertained on the basis of medical history, antidiabetic medication use, glycated hemoglobin ($\geq 6.5\%$), or fasting plasma glucose ($\geq 126 \text{ mg/dl}$). In the CKD group, we included patients aged ≥ 18 years who had an eGFR of $< 60 \text{ ml/min per } 1.73 \text{ m}^2$, $< 5 \text{ g/24 h}$ of proteinuria, BP $< 160/100 \text{ mm Hg}$, and with no change in their BP medications 1 month before enrollment. Controls were aged 30–80 years, with an eGFR $\geq 60 \text{ ml/min per } 1.73 \text{ m}^2$, no proteinuria, and baseline BP values $< 160/100 \text{ mm Hg}$.

We excluded pregnant or breastfeeding women, patients on any insulin sensitizer or medication for treatment of metabolic syndrome, patients with decompensated heart failure, or those who had an acute cardiovascular disease event in the last 6 months. We also excluded patients who had received systemic glucocorticoids or immunomodulators within 1 month of enrollment in the study or had active or severe inflammatory diseases.

The study was approved by the VUMC and VA institutional review boards and informed consent was obtained from all participants.

Study Protocol

Hyperinsulinemic Euglycemic Clamp

Whole-body glucose disposal was evaluated using a glucose clamp after an 8-hour overnight fast, as originally described by DeFronzo *et al.* (14). Blood was drawn, and two peripheral intravenous catheters were placed in both upper extremities. To suppress hepatic gluconeogenesis and augment skeletal and adipose glucose uptake, human regular insulin (50 U/50 ml of 0.9% saline) was infused at a rate of 80 mU/m^2 per minute for patients with CKD and 40 mU/m^2 per minute for control participants. Additionally, 20% dextrose and potassium phosphate were infused to maintain blood glucose concentrations between 90–105 mg/dl and to prevent insulin-induced hypokalemia. Glucose was checked every 5 minutes. Steady state was achieved when blood glucose readings remained stable ($< 10\%$ variation between readings) for > 30 minutes and there were no changes to the glucose infusion rate. In steady-state conditions, the amount of glucose infused is equal to the amount of glucose taken up by the tissue or “M.” The M-value was normalized to body weight and used to calculate the insulin sensitivity index (ISI). Blood was collected at regular intervals during the clamp procedure.

Predictors and Covariates

The main predictors for this study were peripheral and hepatic insulin sensitivity, calculated using clamp-derived ISI and homeostatic model assessment of IR (HOMA-IR), respectively.

ISI was calculated as $M/(G \times \Delta I)$ (15), where M is the glucose disposal rate in milligrams per kilogram per minute (calculated as $[\text{dextrose infusion rate at steady state in milliliters per hour} \times 184] / [\text{weight in kilograms}] \times 60$); G is the mean steady-state glucose concentration in milligrams per deciliter; and ΔI is the difference in plasma insulin concentrations at the beginning and the end of the steady-state period, measured in microunits per milliliter.

HOMA-IR was calculated as fasting serum insulin (in microunits per milliliter) \times fasting serum glucose (in milligrams per deciliter) / 405 (16–19).

Covariates included demographics (age and sex), eGFR, BMI, inflammatory markers (high-sensitivity C-reactive protein and IL6), serum osmolality, adiponectin, and leptin. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (20). Participants were classified as being obese on the basis of the World Health Organization classification (BMI $\geq 30 \text{ kg/m}^2$) and CKD was defined as an eGFR $< 60 \text{ ml/min per } 1.73 \text{ m}^2$.

Serum osmolality was calculated as follows: serum osmolality = $(\text{sodium} \times 2) + (\text{urea} / 2.8) + (\text{glucose} / 18)$ (21). Values for sodium (in milliequivalents per liter), glucose (in milligrams per deciliter), and BUN (in milligrams per deciliter) were obtained from the baseline basic metabolic panel obtained at the start of the hyperinsulinemic euglycemic clamp (HEGC).

Outcomes

The main outcome for this study was serum copeptin, measured using the BRAHMS Copeptin assay (coefficient of variation $< 15\%$ in samples containing 1.5–420 pmol/L copeptin) (22).

Statistical Analyses

The distribution of baseline characteristics of patients with CKD and controls was described across categories of IR (IR versus no IR). IR was defined as an ISI below the 25th percentile (23–25). Between-group differences were examined using the Mann–Whitney *U* test for continuous variables and chi-squared tests for categorical variables. The Pearson correlation coefficient was used to examine the linear relationships between log-transformed copeptin, ISIs (ISI and HOMA-IR), and eGFR.

Copeptin versus Insulin Sensitivity in Patients with CKD versus Controls

A multivariable linear-regression model with robust SEMs was used to investigate the independent relationship between ISI and copeptin adjusted for baseline covariates. To investigate potential heterogeneity of the ISI effect on copeptin levels in patients with CKD versus controls without CKD, we fit a linear model with copeptin as the dependent variable and the following independent variables: ISI, CKD (binary variable, CKD versus controls), and an ISI×CKD interaction term. Linear contrasts were used to obtain the mean difference (β) in copeptin per SD change in ISI among those with CKD and controls after adjustment for demographics, serum osmolality, log IL6, and BMI. The linear models were refit using leptin/adiponectin ratio in lieu of BMI because it is a more robust measure of functional fat that correlates with IR. All analyses were repeated using HOMA-IR in place of ISI as the main predictor.

Copeptin versus Insulin Sensitivity across the eGFR Continuum

A multivariable linear model was fit with copeptin as the dependent variable; ISI and eGFR as main predictors (modeled linearly); an ISI×eGFR interaction term; and demographics, serum osmolality, log IL6, and BMI as covariates. Model-based estimates of mean copeptin were obtained for the range of values of ISI and eGFR for which we had the most data (approximately 2.5th to 97.5th percentile) to improve the reliability of estimates of serum copeptin. These estimates of mean serum copeptin were plotted against both ISI and eGFR using contour plots to display potential interaction between ISI and eGFR for the association with copeptin. The linear models were refit using leptin/adiponectin ratio in lieu of BMI as it is a more robust measure of functional fat that correlates with IR. All analyses were repeated using HOMA-IR in place of ISI.

A two-sided significance level of 0.05 was used for statistical inferences, and all analyses were performed using Stata version 15.1 (StataCorp, College Station, TX).

Results

Baseline Characteristics

The distribution of the baseline characteristics of the 52 patients with CKD and 85 controls included in these analyses, across categories of IR, are detailed in Table 1. In the CKD group, compared with patients with no IR, patients with IR had higher BMI, IL6, serum leptin, fasting plasma insulin, HOMA-IR index, and serum copeptin levels, but lower adiponectin levels. Among controls, although similar patterns were observed for IL6, serum leptin, fasting insulin, and HOMA-IR index, serum copeptin levels in the IR and no IR groups were mostly similar.

Associations between Peripheral IR and Copeptin Levels, Stratified by eGFR

In patients with moderate CKD (eGFR of 30–60 ml/min per 1.73 m²), higher peripheral IR (*i.e.*, lower values of ISI) was significantly correlated with higher values of log copeptin ($r=-0.21, P=0.04$; Figure 1A). Conversely, among controls (eGFR ≥ 60 ml/min per 1.73 m²), the correlation between ISI and log copeptin was minimal ($r=-0.12, P=0.3$). In multivariable models adjusted for age, sex, BMI, serum osmolality, log IL6, and log leptin/adiponectin ratio, a 1 SD decrease in ISI (*i.e.*, increased peripheral IR) was associated with 39% higher serum copeptin levels (Table 2). In controls, similar levels of IR were not associated to differences in serum copeptin levels ($\beta=1\%$; 95% CI, -12% to 15% ; *P* interaction=0.03).

Figure 1B shows a contour plot displaying the differential effects of peripheral IR on serum copeptin levels across levels of eGFR. IR (progressively lower ISI) is associated with higher levels of serum copeptin levels among patients with low eGFR compared with patients with preserved eGFR. For example, a 3 U reduction in ISI, from 6.0 to 3.0 U is associated with an almost 40% higher level of serum copeptin levels among patients with an eGFR of 30 ml/min per 1.73 m², but no difference in serum copeptin among persons with an eGFR of 90 ml/min per 1.73 m² (*P* interaction=0.03).

Associations between HOMA-IR and Copeptin Levels, Stratified by eGFR

Compared with peripheral IR, HOMA-IR scores had a stronger positive correlation with serum copeptin among controls ($r=0.35$) compared with patients with CKD ($r=0.10$; Figure 2A) However, multivariable models adjusted for age, sex, BMI, serum osmolality, log IL6, and log leptin/adiponectin ratio, a 1-SD higher HOMA-IR score was associated with a nonsignificant 17% (95% CI, -5% to 39%) higher serum copeptin level among controls without CKD compared with 5% (95% CI, -10% to 20%) among patients with CKD (*P* interaction=0.32) (Table 3).

As opposed to peripheral IR, the contour plot in Figure 2B shows the effect of hepatic IR, *i.e.*, HOMA-IR scores, on serum copeptin is similar across eGFR levels, as evidenced by the symmetry of the contours and gradients on the plot.

Copeptin, eGFR, and Calculated Serum Osmolality

To assess the relationship between serum osmolality, copeptin, and eGFR, we used the basic metabolic panel obtained on the day of the HEGC to calculate serum osmolality for each patient. The linear relationships between serum copeptin and calculated serum osmolality in patients with reduced ($r=0.32$) and preserved eGFR ($r=0.29$) were similar (Figure 3). However, participants with reduced eGFR had a higher mean calculated serum osmolality (295.0 versus 287.6 mOsm/kg) and higher median copeptin levels (11.2 versus 4.4 pmol/L).

Discussion

We investigated whether IR was associated with higher copeptin levels in nondiabetic patients with stage 3–4 CKD versus controls. Our findings suggest that, in nondiabetic patients with moderate CKD, worsening peripheral IR was associated with higher copeptin levels.

Table 1. Baseline characteristics of patients with CKD and controls across insulin resistance categories

Characteristics	Patients with CKD		Controls	
	IR (n=23) ^a	No IR (n=29)	IR (n=10) ^a	No IR (n=75)
Age (yr), mean (SD)	64 (10)	63 (12)	50 (13)	49 (13)
Black, n (%)	4 (17)	11 (38)	4 (40)	30 (40)
Female, n (%)	10 (44)	6 (21)	6 (60)	47 (63)
BMI (kg/m ²), mean (SD)	33.4 (7.6)	30.0 (5.6)	28.3 (5.3)	29.0 (6.2)
eGFR (ml/min per 1.73 m ²), mean (SD)	45.6 (6.2)	45.6 (11.1)	91.5 (18.4)	96.5 (16.1)
BUN (mg/dl), mean (SD)	24.0 (5.2)	24.7 (11.8)	12.6 (4.5)	12.7 (3.5)
Fasting plasma glucose (mg/dl), mean (SD)	108.7 (14.1)	106.5 (12.8)	104.5 (9.9)	97.7 (10.5)
Plasma sodium (mEq/L), mean (SD)	140.3 (2.4)	140.7 (1.9)	139.7 (1.4)	139.1 (2.0)
Serum osmolality (mOsm/kg), mean (SD)	294.6 (5.9)	295.4 (6.5)	288.8 (4.3)	287.4 (4.4)
Copeptin (pmol/L), median (IQR)	12.2 (8.4–23.1)	9.8 (6.9–16.6)	4.8 (4.2–7.6)	4.4 (3.2–7.3)
Adiponectin (μg/ml), median (IQR)	13.0 (7.3–18.6)	16.0 (9.6–26.5)	10.2 (7.3–16.8)	21.4 (10.4–44.9)
Leptin (ng/ml), median (IQR)	51.1 (31.0–83.0)	20.8 (13.3–34.4)	41.1 (22.3–74.0)	24.8 (15.1–43.2)
Fasting insulin (μU/ml), median (IQR)	25.5 (17.5–31.1)	14.8 (9.7–18.7)	16.0 (8.2–24.6)	8.3 (5.0–11.8)
HOMA-IR index, median (IQR)	6.7 (4.3–9.2)	3.8 (2.7–4.9)	4.0 (2.2–6.0)	2.0 (1.2–2.9)
IL6 (pg/ml), median (IQR)	2.6 (2.0–4.7)	1.9 (1.3–2.7)	2.3 (1.5–3.4)	1.6 (1.0–2.6)

Among patients with CKD, comparisons between those with IR and those with no IR were statistically significant for serum leptin ($P=0.0003$), HOMA-IR ($P=0.002$), and fasting insulin ($P=0.003$). Among controls, these between-group comparisons were also significant for HOMA-IR ($P=0.007$), fasting insulin ($P=0.02$), and fasting glucose ($P=0.02$). IR, insulin resistance; BMI, body mass index; HOMA-IR, homeostasis assessment model of insulin resistance.

^aInsulin resistance defined as insulin sensitivity index less than the 25th percentile (2.6).

The link between vasopressin and plasma glucose is well established. In healthy subjects, the infusion of 20% dextrose suppressed vasopressin (11), whereas the infusion of vasopressin increased plasma glucose (12). In line with these findings, Baylis *et al.* (26) found that hypoglycemia increased vasopressin levels and Vokes *et al.* (11) showed that the presence or absence of insulin modifies vasopressin’s response to changes in serum osmolality. Interestingly, vasopressin is elevated in patients with insulin-dependent diabetes mellitus, independent of changes in serum osmolality (27). These data suggest there is a regulatory pathway between serum glucose levels, insulin, and vasopressin, wherein the lack of insulin leads to elevations in vasopressin. However, the specific mechanism through which

vasopressin and glucose regulate each other remains incompletely explained.

Our current study suggests that CKD-associated peripheral IR is associated with increased copeptin (and, hence, vasopressin) levels. Copeptin is the carboxy terminus byproduct of vasopressin production, which is made at a 1:1 ratio with vasopressin, but has a longer $t_{1/2}$ and is more stable than vasopressin (22,28). Participants with CKD had a slightly higher level of copeptin at baseline (Figure 3). Given the longer $t_{1/2}$ of copeptin, one potential explanation for the elevated levels of copeptin in CKD is a lack of clearance by the kidney. However, even in patients with low eGFR, copeptin levels were low if the participant was insulin sensitive (Figure 1B). This suggests that, even if there is

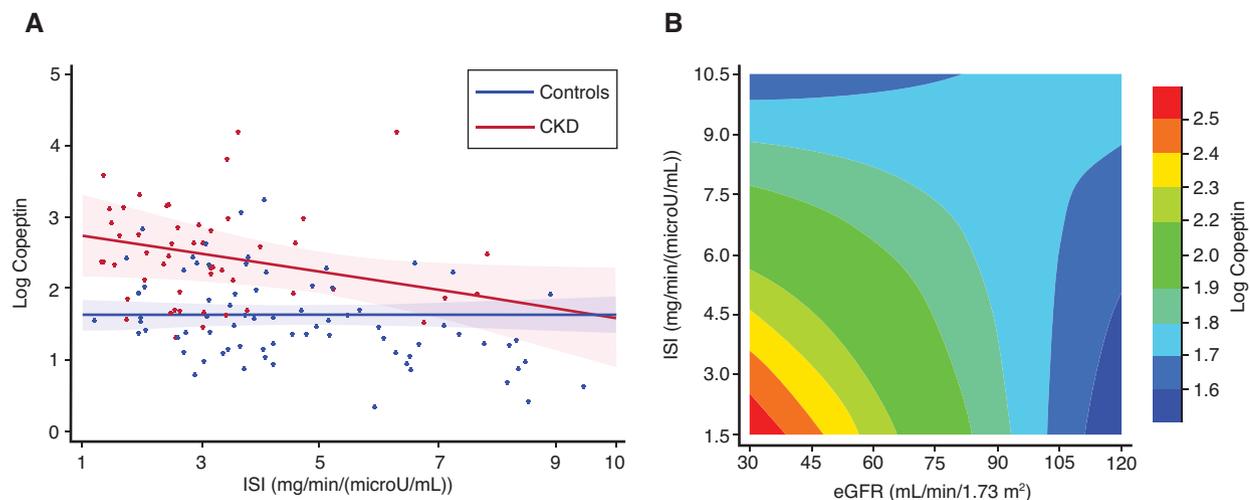


Figure 1. | Relationship between insulin sensitivity index (ISI) and copeptin. (A) Linear relationship between ISI and log copeptin in patients with CKD and controls. (B) Effect of ISI on log copeptin across levels of baseline eGFR.

Table 2. Percentage increase in serum copeptin levels per SD decrease in insulin sensitivity index among patients with CKD and controls

Model	Percentage Change (95% CI)	
	Patients with CKD	Controls
Model 1	34 (0.5 to 68)	0.05 (-7 to 17)
Model 2	39 (3 to 75)	1 (-12 to 15)

Model 1 is adjusted for age, sex, and serum osmolality. Model 2 is adjusted for model 1 variables, BMI, log IL6, and log leptin/adiponectin ratio. *P* interaction (ISI×CKD)=0.03.

decreased clearance of copeptin in CKD, peripheral IR correlates with copeptin levels in patients with an eGFR <60 ml/min per 1.73 m² (Figure 1, Table 2). Therefore, the elevations in copeptin associated to peripheral IR are limited to patients with CKD.

Copeptin is a byproduct of vasopressin production, therefore, the elevated copeptin levels suggest that there are increased levels of vasopressin. Vasopressin is known to be elevated in CKD (6–8), but the elevated levels of vasopressin in CKD are incompletely explained. However, the progressive loss of urinary concentrating ability associated with CKD and the consequent development of vasopressin resistance seem to play a role (5,29–31). Our CKD cohort has higher plasma copeptin levels relative to calculated serum osmolality versus normal controls (Figure 3). Therefore, the elevated levels of copeptin relative to the calculated serum osmolality in our CKD cohort fit with a certain degree of “vasopressin resistance.” However, our findings that link the elevated vasopressin levels in CKD and peripheral IR provides a new dimension to this interaction.

It is known that vasopressin increases blood glucose levels in both humans and rodents (12,32). The hyperglycemic effect of vasopressin is thought to be a combination of activation of glycogen phosphorylase leading to glycogen breakdown and increased circulating glucagon, mediated through the vasopressin 1a receptor (V_{1A}) in the liver and

pancreas, respectively (10,12,33). Increased glucose release by the liver is the hallmark of hepatic IR. However, in CKD, IR is mainly peripheral, *i.e.*, is associated with a decreased uptake of glucose by muscle and fat when stimulated by insulin. In our cohort, peripheral IR was associated with higher levels of copeptin in patients with CKD (Figure 1), whereas hepatic IR was not (Figure 2). The relationship between hepatic IR, copeptin, and eGFR in both our control and CKD groups is similar, where the patients with the most hepatic IR had the highest copeptin levels, independent of renal function. This is not unexpected because higher vasopressin (and, hence, copeptin) levels should theoretically lead to increased hepatic glycogenolysis and gluconeogenesis. In patients with CKD, however, it is unclear whether vasopressin has a direct effect on muscle and fat, which, in turn, causes peripheral IR, or if there is an indirect effect mediated through a separate signaling pathway. The V_{1A} receptor is expressed in both muscle and fat, and vasopressin is known to alter lipid metabolism (34). It is unknown if alterations in V_{1A} signaling at the level of fat or muscle tissue then leads to IR in humans. In rodents, however, the knockout of the V_{1A} receptor led to increased IR and decreased AKT phosphorylation in adipocytes (35). Interestingly, in addition to IR, one of the hallmarks of CKD is the loss of skeletal muscle mass, which is directly linked to IR (36,37). These observations suggest that the mechanism behind IR and vasopressin might involve multiple pathways and tissues, including skeletal muscle.

Our study has several limitations. First, because it is a cross-sectional study, our ability to establish a temporal relationship between CKD, IR, and copeptin is limited. Additionally, although there is an association between copeptin and peripheral IR, it is possible that elevated glucose secondary to IR is driving the increased copeptin level. Although overt diabetes was an exclusion criterion, even subtle persistent elevations in glucose could theoretically increase vasopressin secretion, leading to higher copeptin levels. Another limitation is that we calculated the serum osmolality using the basic metabolic panel obtained at the start of the HEGC instead of using measured osmolality.

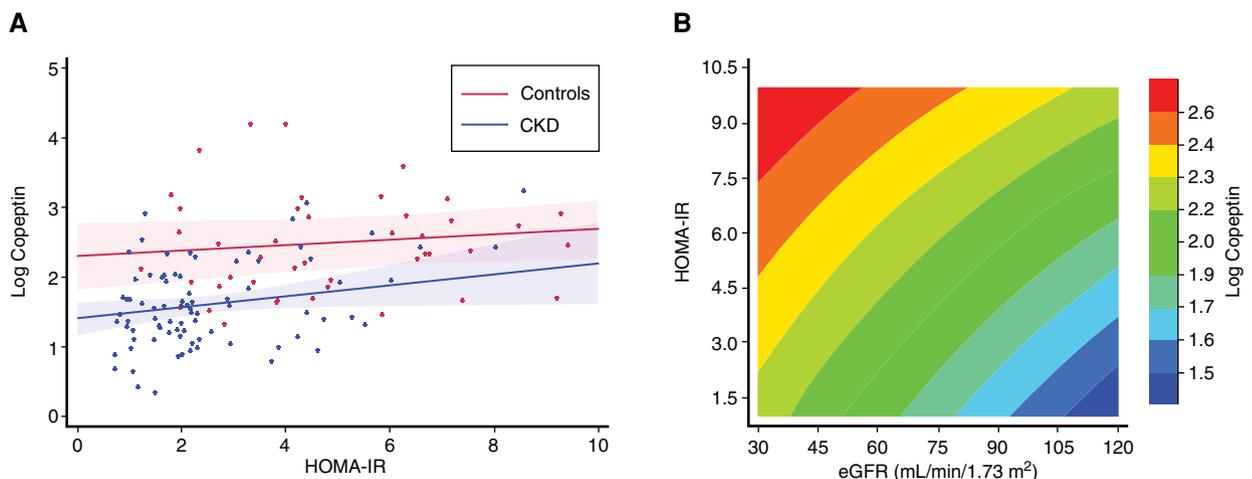


Figure 2. | Relationship between homeostatic model assessment of insulin resistance (HOMA-IR) and copeptin. (A) Linear relationship between HOMA-IR and log copeptin in patients with CKD and controls. (B) Effect of HOMA-IR on log copeptin across levels of baseline eGFR.

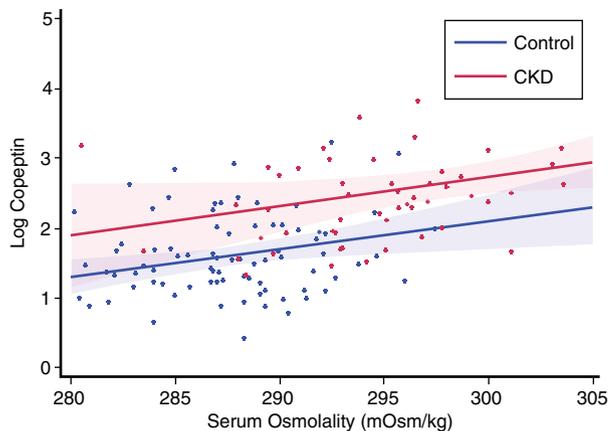


Figure 3. | Linear relationship between log copeptin and calculated serum osmolality in patients with CKD and controls.

Therefore, the possibility exists that there is a discrepancy between the calculated and the measured serum osmolality. The most common cause of a discrepancy between the measured and calculated serum osmolality is the presence of a toxic alcohol. All of our patients were evaluated clinically at the time of the HEGC and none exhibited any signs of intoxication. In spite of these two issues, our data are consistent with prior publications, *i.e.*, that copeptin is elevated but still correlates with serum osmolality in patients with CKD (5,31).

In conclusion, elevated peripheral IR is associated with higher copeptin levels in nondiabetic patients with stage 3–4 CKD. Further research is warranted to determine if there is a feedback loop wherein peripheral IR and copeptin can modify one another, because this could affect progression and management of CKD.

Disclosures

E.A. Akwo reports having other interests in/relationships with the American Heart Association. G. Bhave reports serving as a review editor for *Frontiers in Medicine – Nephrology*. R.C. Harris reports having consultancy agreements with, and receiving research funding from, Bayer; serving on the Bayer Scientific Advisory Board; receiving honoraria from University of California, Los Angeles; and having patents and inventions involving the eNOS db/db mouse.

Table 3. Percentage increase in serum copeptin levels per SD increase in HOMA-IR scores among patients with CKD and controls

Model	Percentage Change (95% CI)	
	Patients with CKD	Controls
Model 1	2 (–11 to 15)	27 (4 to 51)
Model 2	5 (–10 to 20)	17 (–5 to 39)

Model 1 is adjusted for age, sex, and serum osmolality. Model 2 is adjusted for model 1 variables, BMI, log IL6, and log leptin/adiponectin ratio. *P* interaction (HOMA-IR×CKD)=0.32. HOMA-IR, homeostasis assessment model of insulin resistance.

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Author Contributions

E.A. Akwo and J.P. Arroyo were responsible for formal analysis; E.A. Akwo, J.P. Arroyo, G. Bhave, R.C. Harris, T.A. Ikizler, and A.S. Terker reviewed and edited the manuscript; E.A. Akwo and A.M. Hung were responsible for data curation and methodology; A. Alsouqi, J.P. Arroyo, and A.M. Hung were responsible for investigation; J.P. Arroyo wrote the original draft; J.P. Arroyo, G. Bhave, R.C. Harris, T.A. Ikizler, and A.S. Terker conceptualized the study; J.P. Arroyo, A.M. Hung, and T.A. Ikizler were responsible for funding acquisition; G. Bhave, R.C. Harris, and T.A. Ikizler provided supervision; and A.M. Hung and T.A. Ikizler were responsible for project administration.

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