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Original Research

Copeptin and Estimated Insulin Sensitivity in Adults With and Without Type 1 Diabetes: The CACTI Study

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Key Messages

- Copeptin, a surrogate marker of vasopressin, has been found to correlate with cardiovascular and diabetic kidney diseases in both type 1 and type 2 diabetes.
- Copeptin has also been found to be associated with insulin resistance in type 2 diabetes. Our study reveals that copeptin is not related to insulin resistance in type 1 diabetes.

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ABSTRACT

Objectives: Copeptin, a surrogate marker for vasopressin, is elevated in participants with insulin resistance (IR) and type 2 diabetes. Whereas adults with type 1 diabetes also demonstrate elevated copeptin concentrations and IR compared to controls without diabetes, the relationship between copeptin and IR in type 1 diabetes is unclear.
Methods: Participants with (n=209) and without (n=244) type 1 diabetes in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study were assessed for serum copeptin, vitals, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, glycated hemoglobin and lipid panels. Estimated insulin sensitivity (eIS) was calculated by validated equations in participants with and without type 1 diabetes. The relationships among copeptin, IR, waist circumference (WC) and body mass index (BMI) were examined with unadjusted and adjusted linear regression models.
Results: Copeptin was correlated with eIS (R=–0.17, R^2=0.029), WC (R=0.16, R^2=0.026) and BMI (R=0.22, R^2=0.048) for type 1 diabetes and with eIS (R=–0.37, R^2=0.14), WC (R=0.40, R^2=0.16) and BMI (R=0.25, R^2=0.063) in non-type 1 diabetes. In multivariable analysis, copeptin correlated with total cholesterol (beta±SE: –0.12±0.04, p=0.008) and low-density lipoprotein (beta±SE: –0.11±0.04, p=0.01) in type 1 diabetes. In non-type 1 diabetes, copeptin was associated with WC (beta±SE: 0.14±0.04, p=0.0024), BMI (beta±SE: 0.13±0.04, p=0.007) and eIS (beta±SE: –0.14±0.04, p=0.0013).
Conclusions: Copeptin does not correlate with markers of IR in type 1 diabetes but strongly correlates in non-type 1 diabetes. Thus, elevated vasopressin activity and IR appear to be independent risk factors for vascular complications in type 1 diabetes.

Mots clés :
copeptine
insulino-résistance
diabète de type 1
vasopressine

RÉSUMÉ

Objectifs : La copeptine, un marqueur de substitution de la vasopressine, est élevée chez les individus présentant une insulino-résistance (IR) et un diabète de type 2. Alors que les adultes atteints de diabète de type 1 présentent également des concentrations élevées de copeptine et une IR par rapport aux témoins non diabétiques, la relation entre la copeptine et l'IR dans le diabète de type 1 n'est pas claire.

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Méthodes : Les individus avec (n=209) et sans (n=244) diabète de type 1 dans l'étude Calcification de l'artère coronaire dans le diabète de type 1 (CACTI) ont été évalués pour la copeptine sérique, les signes vitaux, le taux de filtration glomérulaire estimé, le rapport urinaire albumine-creatinine, l'hémoglobine glyquée et le profil lipidique. L'estimation de la sensibilité à l'insuline (eIS) a été calculée à l'aide d'équations validées chez les individus avec ou sans diabète de type 1. Les relations entre la copeptine, l'IR, le tour de taille (WC) et l'indice de masse corporelle (BMI) ont été examinées avec des modèles de régression linéaire non ajustés et ajustés.
Résultats : La copeptine s'est trouvée corrélée avec l'eIS (R=–0.17, R^2=0.029), le WC (R=0.16, R^2=0.026) et le BMI (R=0.22, R^2=0.048) pour le diabète de type 1 et avec l'eIS (R=- 0,37, R^2=0,14), le WC (R=0,40, R^2=0,16) et leBMI (R=0,25, R^2=0,063) pour le diabète non associé au type 1. En analyse multivariée, la copeptine s'est trouvée corrélée avec le cholestérol total (beta±SE: –0.12±0.04, p=0.008) et la lipoprotéine de basse densité (beta±SE: –0.11±0.04, p=0.01) dans le diabète de type 1. Dans le diabète non associé au type 1, la copeptine était associée au WC (beta±SE: 0.14±0.04, p=0.0024), le BMI (beta±SE: 0.13±0.04, p=0.007) et l'eIS (beta±SE: –0.14±0,04, p=0,0013).
Conclusions : La copeptine n'est pas corrélée aux marqueurs d'IR dans le diabète de type 1, mais elle y est fortement corrélée dans le diabète non associé au type 1. Ainsi, une activité élevée de la vasopressine et l'IR semblent être des facteurs de risque indépendants de complications vasculaires dans le diabète de type 1.

Introduction

Vasopressin is elevated in people with type 1 and type 2 diabetes mellitus (1). Serum carboxyterminal provasopressin, or copeptin, is a reliable surrogate marker for vasopressin that has a longer half-life (2) and has been shown to be associated with insulin resistance (IR) and vascular complications in adults with obesity and type 2 diabetes (3,4). Elevated serum copeptin can also predict the development of type 2 diabetes (5) and is elevated in subjects with type 2 diabetes, where its presence confers increased risk for both cardiovascular disease (CVD) and diabetic kidney disease (DKD) and for mortality (6,7). Similarly, in type 1 diabetes, we, along with others, have demonstrated that elevated copeptin is associated with CVD and DKD (8,9). People with type 1 diabetes have an increasing prevalence of obesity and IR, which mirrors the recent trends in the general population over the past several decades (10). This alarming development of obesity in people with type 1 diabetes translates to additional risk factors for DKD and CVD (11).

Yet it remains unclear whether elevated copeptin (and, thus, vasopressin) correlates with IR and measures of central adiposity in type 1 diabetes as observed in those with obesity and type 2 diabetes. Given that elevated copeptin and IR both predict vascular complications in type 1 diabetes, it is possible that vasopressin may promote CVD and DKD through the development of IR. Accordingly, we hypothesized that copeptin would correlate with estimated insulin sensitivity (eIS), body mass index (BMI) and waist circumference (WC) in adults with type 1 diabetes.

Methods

Participants

The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study (Clinical Trials NCT00005754) enrolled subjects 19 to 56 years of age, with type 1 diabetes (209) and without type 1 diabetes (244), who were asymptomatic for CVD at the baseline visit between 2000 and 2002 and then were re-examined 3, 6 and 14 years later. The study was approved by the Colorado Multiple Institutional Review Board, and all participants provided informed consent. This particular analysis involves data obtained at the 14-year follow up.

Vital signs and clinical measures

At the first visit, height, weight and WC (measured at the smallest point between the 10th rib and the iliac crest over the bare skin) were recorded, and body mass index (BMI) (weight/height^2) was calculated. Resting systolic blood pressure (SBP) and fifth-phase diastolic blood pressure (DBP) were measured 3 times while the patients were seated, and the second and third measurements were averaged for subsequent analysis.

Laboratory data

After overnight fasts, blood was collected, centrifuged and separated. Serum copeptin levels were measured by ultrasensitive assays (KRYPTOR Compact Plus analyzers; Thermo Fisher Scientific, Waltham, Massachusetts, United States) using the commercial sandwich immunoluminometric assays. The ultrasensitive copeptin assay has a lower limit of detection of 0.9 pmol/L and a functional assay sensitivity of <2 pmol/L. High-performance liquid chromatography was used to measure glycated hemoglobin (A1C) levels (Bio-Rad [variant], Hercules, California, United States); total cholesterol (TC) and triglyceride (TG) concentrations were measured using standard enzymatic methods; high-density lipoprotein cholesterol (HDL-C) was separated using dextran sulfate, and low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula; adiponectin levels were measured by radioimmunoassay. Blood glucose levels were measured by standard methods. Estimated glomerular filtration rates (eGFRs) were calculated by using the Chronic Kidney Disease Epidemiology Collaboration, which is based on serum creatinine levels. Serum creatinine levels were measured according to instructions by using a Roche Mira Plus II analyzer (Basel, Switzerland) until 2006 and then an Olympus AU400e (Shinjuku, Tokyo, Japan) (r=0.9999 between methodologies) traceable to the National Institutes of Standards and Technology standard reference material in the University of Colorado Clinical Translational Research Laboratory. Two timed, overnight urine samples were collected in duplicate, and urine creatinine and albumin were measured (Ria Diagnostics, Bengaluru, India) and averaged to determine a urinary albumin-to-creatinine ratio (UACR).

Estimated insulin sensitivity

The eIS was calculated using an equation developed in a subset of the study cohort (n=87; 40 with type 1 diabetes and 47 normal controls, frequency-matched for age, gender and weight) whose members underwent a 3-stage hyperinsulinemic-euglycemic clamp study to measure insulin sensitivity, which was developed as previously discussed (12,13). For reference, the eIS type 1 diabetes equation is eIS=exp (4.06154 to 0.01317 [waist, cm] to 1.09615 [insulin dose, daily units per kg] + 0.0202 [adiponectin, μg/mL] – 0.00307 [TG, mg/dL] – 0.00733 [DBP, mmHg]); and the eIS nondiabetes

equation is eIS=exp (7.47237 to 0.01275 [waist, cm] – 0.24990 [A1C, %] – 0.01983 [fasting glucose, mg/dL] + 0.01905 [adiponectin, μg/mL] – 0.00324 [TG, mg/dL] – 0.00588 [DBP, mmHg]).

Statistical analysis

Analyses were performed in SAS (v. 9.4 for Windows; SAS Institute, Cary, North Carolina, United States). Variables were checked for the distributional assumption of normality using normal plots. Variables that were positively skewed (e.g. UACR and copeptin) were natural log-transformed for the analyses. Differences in continuous parametric and log-transformed variables between participants with and without type 1 diabetes were examined by using the t test. To examine the relationships among copeptin, eIS, A1C, fasting glucose, WC, BMI, adiponectin, TC, TG, LDL, HDL, SBP, DBP, eGFR and UACR, we ran models with copeptin as a continuous variable. We used multivariable linear regression models for each group (non-type 1 diabetes and type 1 diabetes), adjusted for sex, age, angiotensin-converting enzyme inhibitor (ACEi) use and eGFR. A p value of <0.05 was considered statistically significant. We did not adjust for angiotensin receptor blockers because of their infrequent use (Table 1).

Table 1
Participants' characteristics stratified by type 1 diabetes status

Parameter	Type 1 diabetes (n=209)	Non-type 1 diabetes (n=244)	p value
Age (years)	52.7±9.3	56.5±8.4	<0.001
Sex (% female)	55	52	0.59
Copeptin (pmol/L)	3.5±1.9	2.9±1.9	0.0031
eGFR (mL/s/m^2)	1.4±0.3	1.4±0.2	0.27
Albumin:creatinine ratio (mg/mmol)	0.84±0.45	0.44±0.18	<0.0001
eIS	8.1±4.4	16.2±7.8	<0.0001
BMI (kg/m^2)	27.1±5.0	27.1±5.0	0.90
Fasting blood glucose (mmol/L)	7.9±3.5	4.8±0.8	<0.0001
A1C (%)/(mmol/mol)	7.7±1.1 61±12	5.5±0.5 37±5.5	<0.0001
SBP (mmHg)	123±10	122±13	0.45
DBP (mmHg)	72±8	76±10	<0.0001
Waist circumference (cm)	91.8±13.5	91.1±13.7	0.57
Total cholesterol (mmol/L)	4.1±0.9	4.6±0.9	<0.0001
LDL (mmol/L)	2.2±0.7	2.7±0.8	<0.0001
HDL (mmol/L)	1.5±0.4	1.4±0.4	0.0009
Triglycerides (mmol/L)	0.8±0.3	1.2±0.7	<0.0001
Adiponectin (mcg/mL)	16.2±10.8	10.3±6.7	<0.0001
ACEi use (%)	30.3	3.4	<0.0001
ARB use (%)	4.3	0.4	0.0075

Note: Data are presented as average ± standard deviation unless otherwise noted. *A1C,* glycated hemoglobin; *ACEi,* angiotensin converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *BMI,* body mass index; *DBP,* diastolic blood pressure; *eGFR,* estimated glomerular filtration rate; *eIS,* estimated insulin sensitivity; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *SBP,* systolic blood pressure.

Results

Characteristics stratified by type 1 diabetes status

Table 1 describes the characteristics of participants with and without type 1 diabetes. The most prominent differences between the 2 groups were the higher copeptin concentrations and the lower eIS in those with type 1 diabetes compared to their peers without diabetes. As expected, participants with type 1 diabetes also had higher UACR, fasting glucose and A1C levels but similar eGFRs. Despite being more insulin resistant, participants with type 1 diabetes had better lipid profiles, lower DBPs and higher adiponectin levels in the setting of similar BMIs and WCs. Use of ACEis and angiotensin receptor blockers were significantly higher in those with type 1 diabetes than in those without type 1 diabetes, although the overall use of angiotensin receptor blockers was generally low.

Estimated insulin sensitivity and copeptin

Copeptin concentrations were inversely correlated with eIS in participants with type 1 diabetes and in controls without diabetes (Table 2, Table 3, Figure 1, Figure 2). Copeptin concentrations positively correlated with fasting glucose only in participants without diabetes (Table 3). A1C levels correlated with copeptin levels in controls without diabetes but not in those with type 1 diabetes. In sex-, age-, ACEi use- and eGFR-adjusted analyses, copeptin was significantly associated with A1C levels and fasting glucose in controls without diabetes (Table 3). Copeptin levels were also associated with eIS in controls without diabetes in adjusted models (Table 3). Conversely, copeptin was not associated with eIS in adults with type 1 diabetes in multivariable models (Table 2).

Markers of central adiposity, metabolic syndrome and copeptin

In adults with type 1 diabetes, copeptin correlated positively with WC, BMI, TG and SBP and inversely with HDL, TC and LDL (Table 2). Copeptin did not correlate with adiponectin or DBP. In adjusted models, only TC and LDL were correlated inversely with copeptin (Table 2).

In adults without diabetes, copeptin correlated positively with WC, BMI and inversely with adiponectin and HDL (Table 3). Furthermore, copeptin correlated positively with TG, SBP and DBP and negatively with TC (Table 3). After adjusting for sex, age, ACEi use

Table 2
Univariable and multivariable relationships among copeptin, estimated insulin sensitivity and markers of metabolic syndrome in type 1 diabetes

Variable	Crude R value, R^2 value	p value	Adjusted* Beta±SE, per 1 SD	p value
eIS	–0.17, 0.029	0.02	–0.053±0.05	0.25
A1C	0.04, 0.0016	0.60	–	–
Fasting blood glucose	–0.03, 0.00090	0.70	–	–
Waist circumference	0.22, 0.048	0.002	0.09±0.05	0.09
BMI	0.16, 0.026	0.02	0.07±0.04	0.10
Adiponectin	–0.10, 0.010	0.20	–	–
Total cholesterol	–0.18, 0.032	0.01	–0.12±0.04	0.008
LDL	–0.15, 0.023	0.04	–0.11±0.04	0.01
HDL	–0.18, 0.032	0.01	–0.083±0.05	0.09
Triglycerides	0.15, 0.023	0.04	4.41±3.6	0.22
SBP	0.17, 0.029	0.02	0.067±0.04	0.12
DBP	0.12, 0.014	0.09	–	–

A1C, glycated hemoglobin; *BMI,* body mass index; *DBP,* diastolic blood pressure; *eIS,* estimated insulin sensitivity; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *SBP,* systolic blood pressure; *SD,* standard deviation; *SE,* standard error.

* Adjusted for age, sex, angiotensin-converting enzyme inhibitor use and estimated glomerular filtration rate.

Table 3
Univariable and multivariable relationships among copeptin, estimated insulin sensitivity and markers of metabolic syndrome in non-type 1 diabetes

Variable	Crude R value, R^2 value	p value	Adjusted* Beta±SE, per 1 SD	Model 2 p value
eIS	–0.37, 0.14	<0.0001	–0.14±0.04	0.001
A1C	0.10, 0.01	0.010	0.075±0.04	0.048
Fasting blood glucose	0.22, 0.048	0.0004	0.10±0.04	0.008
Waist circumference	0.40, 0.16	<0.0001	0.14±0.04	0.002
BMI	0.25, 0.063	<0.0001	0.13±0.04	0.007
Adiponectin	–0.30, 0.09	<0.0001	–0.084±0.04	0.04
Total cholesterol	–0.16, 0.026	0.02	–0.035±0.04	0.36
LDL	–0.084, 0.0071	0.20	–	–
HDL	–0.29, 0.084	<0.0001	–0.064±0.05	0.19
Triglycerides	0.14, 0.020	0.03	3.00±4.9	0.54
SBP	0.19, 0.036	0.003	0.064±0.04	0.11
DBP	0.15, 0.023	0.02	0.071±0.04	0.06

A1C, glycated hemoglobin; *BMI,* body mass index; *DBP,* diastolic blood pressure; *eIS,* estimated insulin sensitivity; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *SBP,* systolic blood pressure.

* Adjusted for age, sex, angiotensin-converting enzyme inhibitor use and estimated glomerular filtration rate.

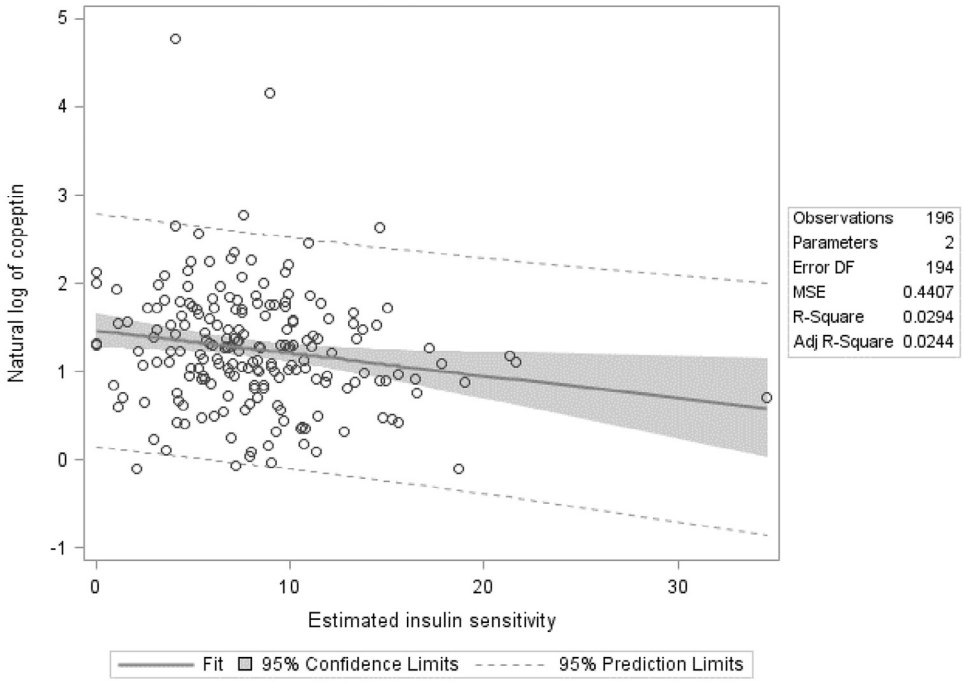

Figure 1. The relationship between the natural log of copeptin and estimated insulin sensitivity in adults with type 1 diabetes; p value=0.02.

and eGFR, WC, BMI and adiponectin remained associated with copeptin (Table 3).

Discussion

Our study is the first to define the relationships between copeptin, a marker of vasopressin, and IR in adults with type 1 diabetes in comparison to those without type 1 diabetes. The major finding of our study is that unlike in non-type 1 diabetes, copeptin did not correlate with eIS, BMI or WC. Furthermore, fasting blood glucose, A1C and adiponectin levels *did* associate with copeptin after age, sex, ACEi use and eGFR adjustments were made in adults without type 1 diabetes, but they did not associate with those features in adults with type 1 diabetes. Overall, our study did not find a relationship between copeptin and markers of IR in type 1 diabetes compared to non-type 1 diabetes despite lower copeptin values in the participants without type 1 diabetes.

Hence, it appears that vasopressin may not play a role in the pathogenesis of IR and obesity in type 1 diabetes compared to the vasopressin observed in patients without type 1 diabetes. Mechanisms for obesity and IR are likely to be unique in those with type 1 diabetes compared to those without type 1 diabetes. For instance, weight gain resulting from prolonged supraphysiologic levels of insulin, along with decreased delivery of insulin to portal circulation, could lead to lower insulin-like growth factor-1 concentrations with subsequent rise in growth hormone and, hence, with consequent IR (14,15). In contrast, people with type 1 diabetes, when matched with those without type 1 diabetes for age and weight, have less hepatic fat content, which correlates with a lower hepatic insulin-to-glucagon ratio (16). Finally, serum uric acid concentrations are associated with IR and metabolic syndrome in people without diabetes, while this association is much weaker in people with type 1 diabetes (17). Therefore, vasopressin may similarly have a varying role in type 1 diabetes compared to non-type 1 diabetes in terms of markers of IR and central obesity.

Animal research has advanced our understanding of the role of vasopressin in the development of IR. Studies in lean and obese Zucker rats reported that chronic vasopressin infusion worsened

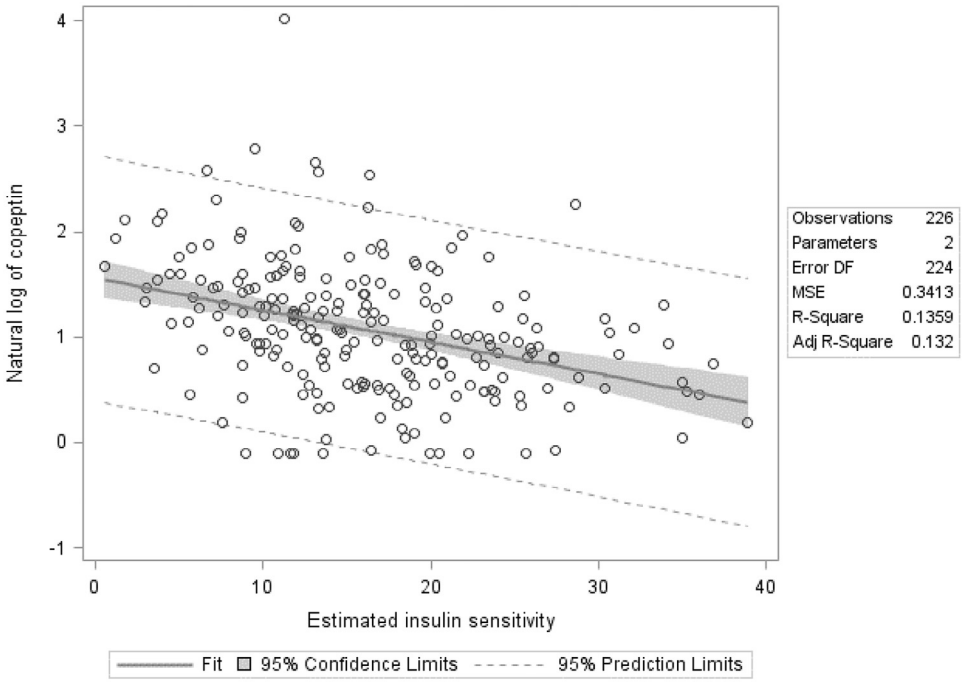

Figure 2. The relationship between the natural log of copeptin and estimated insulin sensitivity in adults without diabetes; p value<0.0001.

glycemic control and, in obese rats, promoted hyperinsulinemia and glucose intolerance, whereas a hydration-associated reduction in vasopressin resulted in decreased liver steatosis (18). Vasopressin 1a and 1b (V1a and V1b) are found in metabolically important tissues, including corticotropic cells in the pituitary, islet cells regulating insulin and glucose, and adipose, liver and adrenal tissues, and have been found to play roles in glucose and lipid metabolism (19). In particular, V1b knockout mice have improved glucose tolerance and insulin sensitivity as well as diminished lipolysis compared to wild-type mice (20,21). In addition, polymorphisms in the V1b receptor in humans have been linked to diabetes and obesity. Finally, a V1b antagonist, SSR149415, ameliorated glucose excursions in obese or ob/ob mice (mice with mutations in the leptin gene) in a pyruvate tolerance test, a test utilizing pyruvate to induce hepatic gluconeogenesis (22). Thus, targeting the vasopressinergic system may be a promising target to improve IR in type 2 diabetes and in obese patients without diabetes, although our study suggests that this strategy would not be likely to be as useful in type 1 diabetes for IR management.

Another conclusion we can draw is that although vasopressin and IR drive vascular complications in type 1 diabetes, their roles are likely to be independent from each other. The association between copeptin and IR is lost after adjusting for age, sex, ACEi use and eGFR in those with type 1 diabetes as opposed to controls without diabetes, so that suggests that vasopressin and IR have distinct but equally important roles in the development of vascular complications in type 1 diabetes.

However, copeptin did associate with lower TC and LDL in adults with type 1 diabetes, and there was a trend for lower HDL after adjustments for sex and age. This was not noted in our patients without diabetes, although with significantly lower copeptin values, this effect on lipid metabolism might be less apparent at lower concentrations. Similar findings of lower TC, HDL and LDL and higher TG levels in association with copeptin have been found in individuals with type 1 diabetes, polycystic ovarian syndrome and type 2 diabetes (23–25). It has been shown recently in animal models that vasopressin has an antilipolysis effect through inhibiting hormone-sensitive lipase and blocking beta oxidation (26), and this antilipolysis effect has also been observed in humans (27). Hence, it is plausible that vasopressin may play a role in lipid metabolism.

Our study does not address the relationship between copeptin and markers of DKD, including eGFR and UACR, because that was discussed in a previous study of this population, which showed a strong correlation of copeptin with eGFR and UACR in type 1 diabetes (8,28). Thus, our study adds to these data by suggesting that vasopressin's role in CVD in type 1 diabetes is likely to be due, in part, to the development of DKD but does not play a significant role in IR that may also lead to CVD in type 1 diabetes. In addition, ACEi use may be a plausible mechanism for affecting vasopressin levels because angiotensin II has been found to regulate vasopressin secretion through the supraoptic nucleus in the hypothalamus (29). It has been speculated by some that ACEi use can, paradoxically, cause the syndrome of inappropriate antidiuretic hormone because more angiotensin 1 is available to be converted in the brain into angiotensin II, but the true mechanism is not known (30). No direct study has looked at whether ACEi use affects copeptin levels, and conflicting data in type 2 diabetes show no association between copeptin levels and ACEi use (6). Mixed results have been shown in type 1 diabetes; in 1 cohort, copeptin levels were not associated, but in another cohort, ACEi use did associate with higher levels of copeptin (9).

This study has important limitations worth mentioning, including the cross-sectional design, which prohibited implications of causality. Also, the sample size is relatively small. Therefore, these analyses should be considered as generations of hypotheses. Strengths of the study include data concerning adults with and without type 1 diabetes. Longitudinal studies are needed for better definition of the role vasopressin plays in the pathogenesis of IR in adults with and without type 1 diabetes.

Conclusions

Our study is the first to define the relationship between copeptin, a surrogate for vasopressin, and markers of IR in adults with and

without type 1 diabetes. In adults without type 1 diabetes, we found strong associations with traditional metabolic measures, such as BMI, WC, FBG and eIS. Despite having significantly higher concentrations of copeptin and lower eIS compared to patients without diabetes, copeptin was not associated with eIS in patients with type 1 diabetes. Therefore, it appears that IR and elevated vasopressin activity are independent risk factors for DKD and CVD in adults with type 1 diabetes.

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Author Disclosures

Conflicts of interest: None.

Author Contributions

TJ researched, wrote, contributed to discussions, analyzed data and reviewed and edited the manuscript; PB performed research, contributed to discussions, analyzed data and reviewed and edited the manuscript; MR designed the CACTI study, performed research, contributed to discussions and reviewed and edited the manuscript; RJJ and RS contributed to discussions and reviewed and edited the manuscript; JKSB performed research, wrote, analyzed data, contributed to discussions and reviewed and edited the manuscript.

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