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Elevated copeptin is associated with atherosclerosis and diabetic kidney disease in adults with type 1 diabetes

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Abstract

Background—Vasopressin exerts important cardio-renal effects, but remains problematic to measure. Copeptin is a more stable peptide derived from the same precursor molecule. We examined the associations between copeptin, coronary artery calcium (CAC), albuminuria and impaired glomerular filtration rate (GFR) in adults with type 1 diabetes (T1D).

Methods—Participants with (n=209) and without T1D (n=244) in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study were assessed for serum copeptin, CAC measured using 128-slice spiral CT, urinary albumin-to-creatinine ratio (UACR) and eGFR calculated by CKD-EPI creatinine. Impaired GFR was defined as eGFR <60 mL/min/1.73 m², albuminuria as UACR ≥30 mg/g, high and very high CAC score as ≥100 and ≥300 AU, and elevated copeptin as >13 pmol/L (>97.5th percentile for healthy adults). Unadjusted and adjusted (age, sex, HbA1c, SBP and LDL-C) logistic models were applied to examine the relationships.

Results—Participants with T1D had greater ultrasensitive copeptin concentrations than nondiabetics (3.5 [95% CI 2.3–3.8] vs. 2.8 [2.7–3.1], p=0.003). In participants with T1D, elevated copeptin was associated with greater odds of impaired eGFR (OR: 18.52, 95% CI 4.03–85.02), albuminuria (10.55, 2.24–49.62), high CAC (6.61, 1.39–31.31) and very high CAC (6.24, 1.51–

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25.90) in multivariable models. Similar linear relationships were obtained with ultrasensitive copeptin, eGFR, UACR, CAC volume and CAC score in adjusted models.

Conclusion—In this cross-sectional analysis, copeptin was strongly associated with diabetic kidney disease and coronary atherosclerosis in adults with T1D. Further research is needed to determine whether these relationships hold true longitudinally in people with T1D.

Introduction

Cardio-renal complications are the major causes of mortality in type 1 diabetes (T1D) [1], with diabetic kidney disease (DKD) being the single most important cause of renal failure in the Western world [2]. Coronary artery calcification (CAC), a marker of coronary artery plaque burden, predicts coronary events in T1D [2]. The presence and progression of CAC are useful surrogate CAD end points in evaluating novel CAD risk factors [2].

Arginine vasopressin (AVP) plays an essential role in regulation of volume status and exerts important renal and cardiovascular effects [3]. Measuring AVP is unfortunately associated with technical difficulties, due to its relatively small size and short half-life. Copeptin is a more stable peptide derived from the same precursor molecule as AVP, and is recognized as a surrogate marker for AVP useful in the assessment of fluid and osmosis status in various diseases [3].

AVP concentrations are higher in people with diabetes compared with healthy counterparts [4], and people with T1D are thought to have an exaggerated response to AVP [5]. High concentrations of plasma AVP are known to stimulate V1a receptors preferentially [5], which may contribute to the cardiovascular complications associated with diabetes. Associations between copeptin, CAD and DKD have been demonstrated in adults with type 2 diabetes (T2D) [6, 7], but these relationships have to our knowledge not yet been examined in adults with T1D. Accordingly, we sought to examine the associations between copeptin, elevated coronary artery calcium (CAC), albuminuria and impaired GFR ($<60\text{mL}/\text{min}/1.73\text{m}^2$) in adults with T1D.

Methods

The CACTI Study enrolled subjects 19–56 years old, with and without T1D, who were asymptomatic for cardiovascular disease (CVD) at the baseline visit in 2000–2002 and then were re-examined 3, 6 and 12 years later. The study was approved by the Colorado Multiple Institutional Review Board and all participants provided informed consent. This cross-sectional pilot study examines the relationship between copeptin and cardio-renal complications at the 12-year follow-up visit. All participants with ($n=209$) and without ($n=244$) T1D and data available at visit 4 as of 12/1/2015 to assess serum copeptin and ultrasensitive copeptin, CAC score measured by 128-slice spiral computed tomography, eGFR calculated by CKD-EPI creatinine and urinary albumin-to-creatinine ratio (UACR), were included in this study. Impaired GFR was defined as $\text{eGFR} < 60\text{mL}/\text{min}/1.73\text{m}^2$, albuminuria was defined as $\text{UACR} \geq 30\text{ mg/g}$, and high and very high CAC score were defined as ≥ 100 and ≥ 300 Agatston units (AU) respectively.

After an overnight fast, blood was collected, centrifuged, and separated. Copeptin was measured by standard and ultrasensitive assays on KRYPTOR and KRYPTOR Compact Plus analyzers using the commercial sandwich immunoluminometric assays (Thermo Fisher Scientific, Waltham, MA). The standard copeptin assay is used to detect elevated copeptin ($>13\text{pmol/L}$), and has a lower detection limit of 4.8pmol/L . Elevated copeptin was defined as $>13\text{pmol/L}$, which is $>97.5^{\text{th}}$ percentile for healthy adults [8]. The ultrasensitive copeptin assay has a lower limit of detection of 0.9pmol/L and a functional assay sensitivity of $<2\text{pmol/L}$. High performance liquid chromatography was used to measure HbA1c (HPLC, BioRad variant) and total plasma cholesterol and triglyceride (TG) levels were measured using standard enzymatic methods, HDL-C was separated using dextran sulfate and LDL-C was calculated using the Friedewald formula.

Statistical Analysis

Analyses were performed in SAS (version 9.4 for Windows; SAS Institute, Cary, NC). Variables were checked for the distributional assumption of normality using normal plots. Variables that were positively skewed (e.g. ACR, copeptin and US copeptin) were natural log-transformed for the analyses. Differences in continuous parametric and log-transformed variables between participants with and without T1D were examined with the *t*-test. Wilcoxon two-sample test used to examine the differences in CAC score between participants with and without T1D, as observations with CAC scores equal to 0 limits meaningful log-transformation.

To examine the relationships between copeptin, CAC and DKD, we ran models with US copeptin as a continuous variable, in addition to elevated copeptin defined as copeptin $>13\text{pmol/L}$. We applied multivariable logistic regression models, adjusted for age, sex, HbA1c, SBP and LDL-C (American Diabetes' Association ABC risk factors) to evaluate the relationships between US copeptin, elevated copeptin, albuminuria, impaired GFR and high and very high CAC. Unadjusted and adjusted generalized linear models were also applied to examine the relationships between US copeptin, UACR, eGFR and CAC score. Finally, we stratified participants according to tertiles of US copeptin (high: 4.34 , mid: 2.73 – 4.34 , low: $<2.73\text{pmol/L}$), and examined UACR, eGFR and CAC scores across tertiles. A P-value < 0.05 was considered statistically significant.

Results

Participants' characteristics stratified by T1D status are presented in Table 1. Participants with T1D were younger and had greater UACR and CAC scores than their normoglycemic peers (Table 1). Ultrasensitive copeptin was greater in participants with T1D compared to those without (3.5 [95% CI 2.3 – 3.8] vs. 2.8 [95% CI 2.7 – 3.1], $p=0.003$), and the difference remained significant after adjusting for age, sex and eGFR (3.6 [95% CI 3.3 – 3.9] vs. 2.9 [95% CI 2.7 – 3.2], $p=0.0008$). Elevated copeptin was evident in 6% of participants with T1D. Furthermore, high CAC was evident in 34% and very high CAC in 21% of participants with T1D. CKD was demonstrated in 9% and albuminuria in 14% of participants with T1D (Table 1).

In participants with T1D, ultrasensitive copeptin was positively associated with UACR ($\beta \pm \text{SE}$: 0.83 ± 0.14 , $p < 0.0001$), negatively associated with eGFR ($\beta \pm \text{SE}$: -12.03 ± 1.78 , $p < 0.0001$), positively associated with both CAC score ($\beta \pm \text{SE}$: 345.74 ± 99.07 , $p = 0.0006$) and CAC volume ($\beta \pm \text{SE}$: 291.58 ± 80.23 , $p = 0.0004$) in separate multivariable models. One standard deviation (SD) increase in natural log of ultrasensitive copeptin was associated with greater odds of albuminuria, impaired GFR, high CAC and very high CAC in unadjusted and adjusted models (Table 2). We also stratified participants according to tertiles of ultrasensitive copeptin, and participants in the highest tertile ($> 4.34 \text{ pmol/L}$) had higher CAC score (Figure 1), lower eGFR (Figure 2) and higher UACR (Figure 3) compared to participants in the lowest tertile ($< 2.73 \text{ pmol/L}$).

The limited number of participants with elevated copeptin ($n = 13$) [$> 13 \text{ pmol/L}$] had significantly greater odds of albuminuria, impaired GFR, high CAC and very high CAC, and these associations remained significant in separate multivariable models adjusting for age, sex, HbA1c, SBP and LDL-C (Table 2).

Discussion

Our cross-sectional data demonstrate higher ultrasensitive copeptin concentrations in adults with compared to adults without T1D. Furthermore, we show strong associations between copeptin, DKD and atherosclerosis independent of other important risk factors in adults with T1D. While copeptin has been linked with DKD and cardiovascular mortality in adults with T2D, limited data exist for adults with T1D. Elevated copeptin, i.e. above the 97.5th percentile for a healthy reference population [8], was associated with a 7-fold increased odds of CAC ≥ 300 . A CAC score ≥ 300 has been shown to confer a 10-fold increased risk of cardiovascular events [9]. Albeit cross-sectional, these observations propose a potential role of vasopressin in the pathogenesis of cardiorenal complications in adults with T1D consistent with data in nondiabetics and adults with T2D, which warrants further investigation.

Copeptin is secreted with AVP from the neurohypophysis and appears to quantify endogenous stress in a variety of medical conditions including acute myocardial infarction [10], in addition to conferring risk of cardiovascular mortality [7] and DKD in T2D. AVP concentrations are higher in people with T1D compared with healthy counterparts [4]. While vasopressin has classically been thought of as a hormone primarily involved in urinary concentration, vasopressin may also have multiple other effects, including raising systemic and glomerular blood pressure, stimulating vasoconstriction, mediating gluconeogenesis and glucagon release, and possibly even stimulating fat accumulation. Vasopressin can also accelerate kidney disease in experimental models and induce proteinuria in humans [3].

Ultrasensitive copeptin and elevated copeptin were strongly associated with the prevalence of albuminuria, impaired GFR, high, and very high CAC in our cohort of adults with T1D. Copeptin was related to the cardiorenal complications independently of conventional ABC risk factors (HbA1c, SBP, LDL-C), which may suggest that the copeptin mediates disease independent of glycemia, dyslipidemia and hypertension.

Our study does have important limitations including the small sample size and crosssectional design which prevents determination of causality, and whether the association holds true longitudinally. For these reasons the data should be viewed as hypothesis generating. Results from this study may also not be generalizable to youth with T1D. The participants with T1D without complete data at 12-year follow-up had similar duration (23 ± 9 vs. 24 ± 9 years, $p=0.57$), eGFR (103 ± 29 vs. 103 ± 24 mL/min/1.73m², $p=0.87$) and prevalence of high (11 vs. 10%, $p=0.68$) and very high CAC (6 vs 3%, $p=0.16$) at baseline as those with complete data, but worse ACR (12 [95% CI: 10–15] vs 8 [7–10] mg/g, $p=0.004$) and glycemic control (8.0 ± 1.3 vs. $7.7\pm 1.1\%$, $p=0.0004$) at baseline which may bias our results to the null as less healthy participants with T1D were not included in the analyses.

In conclusion, adults with T1D had greater concentrations of US copeptin than their normoglycemic peers, and copeptin was strongly associated with increased prevalence of DKD and atherosclerosis in adults with T1D, independent of conventional risk factors. Whether the relationship between copeptin and DKD and atherosclerosis is causal or secondary to an unknown confounder remains unknown. AVP is a potential target for treatment of cardiorenal complications in T1D with the availability of vaptans and lifestyle changes (e.g. increased water intake). Longitudinal research in T1D is required to better determine whether copeptin plays a causal role in the development of DKD and atherosclerosis in adults with T1D.

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References

1. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association. *Circulation*. 2014
2. Snell-Bergeon JK, Maahs DM. Diabetes: Elevated risk of mortality in type 1 diabetes mellitus. *Nature reviews Endocrinology*. 2015; 11:136–138.
3. Bardoux P, Martin H, Ahloulay M, et al. Vasopressin contributes to hyperfiltration, albuminuria, and renal hypertrophy in diabetes mellitus: study in vasopressin-deficient Brattleboro rats. *Proceedings of the National Academy of Sciences of the United States of America*. 1999; 96:10397–10402. [PubMed: 10468619]
4. Zerbe RL, Vinicor F, Robertson GL. Plasma vasopressin in uncontrolled diabetes mellitus. *Diabetes*. 1979; 28:503–508. [PubMed: 108167]
5. Coiro V, Capretti L, Speroni G, et al. Abnormal arginine-vasopressin responses to metoclopramide and insulin-induced hypoglycemia in type I diabetes mellitus. *Hormone research*. 1990; 33:227–232. [PubMed: 2289781]
6. Fenske W, Wanner C, Allolio B, et al. Copeptin levels associate with cardiovascular events in patients with ESRD and type 2 diabetes mellitus. *J Am Soc Nephrol*. 2011; 22:782–790. [PubMed: 21415158]
7. Riphagen IJ, Boertien WE, Alkhalaf A, et al. Copeptin, a Surrogate Marker for Arginine Vasopressin, Is Associated With Cardiovascular and All-Cause Mortality in Patients With Type 2 Diabetes (ZODIAC-31). *Diabetes Care*. 2013

8. Keller T, Tzikas S, Zeller T, et al. Copeptin improves early diagnosis of acute myocardial infarction. *J Am Coll Cardiol.* 2010; 55:2096–2106. [PubMed: 20447532]
9. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med.* 2008; 358:1336–1345. [PubMed: 18367736]
10. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med.* 2009; 361:858–867. [PubMed: 19710484]

Highlights

- Vasopressin is associated with cardio-renal complications in type 2 diabetes (T2D).
- Limited data on this relationship in type 1 diabetes (T1D).
- Copeptin is a more stable peptide derived from the same precursor molecule as vasopressin.
- Our data suggest that copeptin is associated with atherosclerosis and diabetic kidney disease in T1D.

Figure 1.
CAC Scores across Tertiles of Ultrasensitive Copeptin

Figure 2.
eGFR across Tertiles of Ultrasensitive Copeptin

Figure 3.
Natural Log of ACR across Tertiles of Ultrasensitive Copeptin

Table 1

Participants' Characteristics Stratified by T1D Status

Variables	CACTI Participants		P-value
	T1D (n=209)	Controls (n=244)	
Age (years)	53±9	57±8	<0.0001
Gender (Female)	55%	52%	0.59
Duration (years)	38±9	--	--
HbA1c (%)	7.7±1.1	5.5±0.5	<0.0001
HbA1c (mmol/mol)	61±12	37±6	<0.0001
SBP (mm Hg)	123±10	122±13	0.45
DBP (mm Hg)	72±8	76±10	<0.0001
LDL-C (mg/dl)	86±27	104±29	<0.0001
BMI (kg/m ²)	27±5	27±5	0.90
Ultrasensitive copeptin*	3.5 (3.2–3.8)	2.9 (2.7–3.1)	0.003
Elevated copeptin (≥13pmol/L) [%]	6% (13)	4% (10)	0.34
CAC score (AU)**	9 (0–179)	0 (0–46)	0.0002
High CAC (≥100 AU) [%]	33% (58)	16% (35)	<0.0001
Very high CAC (≥300 AU) [%]	21% (37)	9% (19)	<0.0001
eGFR (mL/min/1.73m ²)	84±19	82±13	0.27
eGFR<60mL/min/1.73m ² [%]	10% (20)	6% (14)	0.12
UACR (mg/g)*	7 (6–9)	4 (3–4)	<0.0001
Albuminuria (≥30mg/g) [%]	14% (24)	0% (0)	<0.0001

* Geometric mean, 95 CI

** Median, P25-75

Table 2

Multivariable logistic models examining relationships between copeptin, DKD and CAC

	Albuminuria (≥ 30mg/g) [n=24]	Impaired GFR (<60mL/min/1.73m²) [n=20]	High CAC (≥ 100 AU) [n=58]	Very high CAC (≥ 300 AU) [n=37]
<i>Presence or absence of elevated copeptin</i>				
Copeptin ≥ 13 pmol/L (yes)	11.92 (3.07–46.28) P=0.0003	10.96 (3.24–37.07) P=0.0001	7.71 (2.03–29.26) P=0.003	7.17 (2.19–23.52) P=0.001
Copeptin ≥ 13 pmol/L * (yes)	10.55 (2.24–49.62) P=0.003	18.52 (4.03–85.02) P=0.0002	6.61 (1.39–31.31) P=0.02	6.24 (1.51–25.90) P=0.01
<i>Copeptin as continuous variable with ultrasensitive assay</i>				
Ln copeptin (per 1 SD [0.69])	2.24 (1.38–3.64) P=0.001	2.21 (1.38–3.54) P=0.001	1.78 (1.23–2.56) P=0.002	1.85 (1.24–2.76) P=0.003
Ln copeptin * (per 1 SD [0.69])	2.13 (1.24–3.65) P=0.006	3.12 (1.67–5.86) P=0.0004	1.74 (1.10–2.76) P=0.02	1.71 (1.08–2.73) P=0.02

* Adjusted for age, sex, HbA1c, LDL-C and SBP