Original Report: Patient-Oriented, Translational Research

American Journal of Nephrology

Am J Nephrol 2016;44:22–28
DOI: 10.1159/000447522

Received: January 20, 2016
Accepted: June 7, 2016
Published online: June 28, 2016

Increased Levels of Copeptin, a Surrogate Marker of Arginine Vasopressin, Are Associated with an Increased Risk of Chronic Kidney Disease in a General Population

Irina Tasevska[a, c] Sofia Enhörning[a, c] Anders Christensson[b, d]
Margaretha Persson[a, c] Peter M. Nilsson[a, c] Olle Melander[a, c]

Departments of [a]Internal Medicine and [b]Nephrology, Skåne University Hospital, Departments of [c]Clinical Sciences and [d]Nephrology, Lund University, Malmö, Sweden

Key Words
Chronic kidney disease · Copeptin · Estimated glomerular filtration rate · Epidemiology

Abstract
Background: Our aim was to test if plasma copeptin, a stable surrogate marker of arginine vasopressin, predicts decline of glomerular filtration rate (GFR) and risk of chronic kidney disease (CKD). ***Methods:*** We measured copeptin and renal function at the Malmö Diet and Cancer Cardiovascular Cohort baseline exam and reassessed renal function after a follow-up time of 16.6 ± 1.5 years (n = 3,186). Furthermore, we defined CKD based on an estimated GFR (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) <60 (CKD_60_{MDRD}), <45 (CKD_45_{MDRD}) and <30 (CKD_30_{MDRD}) ml/min/1.73 m^2. ***Results:*** After multivariate adjustment (gender, age, baseline eGFR, smoking status, systolic blood pressure, antihypertensive treatment and follow-up time), copeptin (beta-coefficient per 1 SD increment of copeptin) was independently associated with significantly greater annual decline of eGFR (ml/min/1.73 m^2) according to the MDRD formula (OR 0.057, 95% CI 0.022–0.093; p = 0.001) as well as according to the CKD Epidemiology Collaboration (CKD-EPI) formula (OR 0.050, 95% CI 0.022–0.077; p < 0.001). Each SD increment of copeptin independently predicted incident CKD_60_{MDRD} (OR 1.19, 95% CI 1.04–1.36; p = 0.010), CKD_45_{MDRD} (OR 1.33, 95% CI 1.04–1.71; p = 0.026) and CKD_30_{MDRD} (OR 3.69, 95% CI 1.41–9.66; p = 0.008). The relationship between copeptin and CKD defined by CKD-EPI gave similar results. ***Conclusion:*** Our data suggest that increased levels of copeptin independently predict decline in eGFR and greater risk of new-onset CKD.

Introduction

Arginine vasopressin (AVP) is a peptide released in response to increased plasma osmolality or decreased blood pressure. It is released from the posterior pituitary gland and exerts antidiuresis by acting on the vasopressin 2 receptors (V2R) in the renal tubules [1]. AVP is an unstable peptide, both in vivo and ex vivo, and has a short half-life of 5–20 min [2], which requires complicated handling when sampling a patient's blood. When AVP is produced, the precursor protein leaves a cleavage product as its C-terminal part termed copeptin, which is expressed in a 1:1

KARGER

E-Mail karger@karger.com
www.karger.com/ajn

Irina Tasevska
Department of Internal Medicine
Skåne University Hospital
SE–20502 Malmö (Sweden)
E-Mail tasevskairina@gmail.com

ratio with AVP. Copeptin is a more stable molecule in plasma and is eliminated partially by renal excretion. It can therefore be used as a surrogate marker of AVP. An overactivation of the AVP system, measured as elevated copeptin levels in plasma, has been linked to cardiometabolic risk factors [3, 4] and the ability to predict development of type 2 diabetes independent of known diabetes risk factors [5, 6]. In experimental studies performed on rodent models of diabetes mellitus, results have shown that infusion of AVP induces hypertension, glomerular hyperfiltration, albuminuria and glomerulosclerosis [7] thus suggesting a role of AVP in the pathogenesis of deterioration of renal function. In line with these findings, it was found that elevated levels of copeptin at baseline were associated with greater decline in estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes during long-term follow-up [8] as well as with the renal end point of doubling of plasma creatinine in patients with both type 2 diabetes and albuminuria [9]. In addition, in type 2 diabetes patients treated in primary healthcare, increased levels of copeptin were associated with elevated risk of cardiovascular and all-cause mortality [10], findings in line with 2 of our own previous studies showing strong independent association between copeptin and cardiovascular morbidity and mortality, especially in patients with diabetes [11, 12]. In healthy kidney donors, eGFR decreased significantly following donation but copeptin remained unchanged, suggesting that AVP, as measured by copeptin, may in fact be causally related to the decline of eGFR rather than just being a small molecule marker of eGFR [13]. Here, we investigated if copeptin independently predicts decline of eGFR and development of chronic kidney disease (CKD) in a large population-based study.

Methods

The population for our study is derived from the population-based Malmö Diet and Cancer Study (MDCS). During 1991–1996, a total number of 28,098 people born between 1923–1945 and 1923–1950 participated in the baseline examination. All the study protocols were approved by the regional Ethics Committee of Lund University and all the participants provided written informed consent. A random number of 6,103 subjects participated in additional examinations to study the epidemiology of carotid artery disease with ultrasonography of carotid arteries, with a special interest in intima media thickness within the MDCS Cardiovascular Cohort (MDCS-CC) [14]. Out of these subjects, 5,400 people came fasting to also provide fasting blood samples. From the total of 5,400 subjects who donated fasting blood, we were able to determine copeptin in 5,252 subjects. Between 2007 and 2012 (mean follow-up time 16.6 ± 1.5 years), 3,186 out of the 5,252 individuals in the MDCS-CC were re-examined including a determination of eGFR. These were the subjects used in our study.

At the re-examination, new blood samples were taken including creatinine and cystatin C as well as height and weight were measured. Copeptin at baseline was measured in plasma samples that had been stored in –80°C. Plasma level of copeptin was then related to development of CKD. We calculated eGFR based on both the Modification of Diet in Renal Disease (MDRD) formula and the CKD Epidemiology Collaboration (CKD-EPI) formula, as detailed below. Also, copeptin was related to the continuous decline in eGFR over time, calculated as eGFR during baseline subtracted from eGFR during follow-up and divided by the follow-up time in years (i.e., annual decline of eGFR in ml/min/1.73 m^2).

Clinical Examination and Assays

Participants underwent a registration of medical history, a physical examination and laboratory assessment. The participants' weight (kg) and height (cm) were measured by trained nurses. Blood pressure (mm Hg) was measured using an oscillometric device twice after 10 min of rest in the supine position. Cigarette smoking was elicited by a self-administered questionnaire, with current cigarette smoking defined as any use within the past year. Diabetes mellitus was defined as fasting plasma glucose of ≥7.0 mmol/l, a self-reported physician diagnosis of diabetes or use of anti-diabetic medication. Measurement of fasting serum total cholesterol, HDL cholesterol, triglycerides, creatinine and cystatin C was made according to standard procedures at the Department of Clinical Chemistry, Skåne University Hospital, Malmö. Plasma creatinine was analyzed with the Jaffé method and traceable to the International Standardization with isotope dilution mass spectrometry. The same technique was used for measuring plasma creatinine at baseline and at the follow-up. Plasma cystatin C was measured using a particle-enhanced immunonephelometric assay (N Latex Cystatin; Dade Behring, Deerfield, Illinois) at baseline and follow-up. The values of cystatin C were not standardized because they were analyzed before the introduction of the world calibrator in 2010. The reference value for the method was 0.53–0.95 mg/l. eGFR was calculated from the MDRD formula for creatinine [15] and from the CKD-EPI formula for both creatinine and cystatin C [16]. LDL cholesterol was calculated according to Friedewald's formula. We measured copeptin in fasted EDTA plasma using a commercially available assay in the chemiluminescence/coated tube format (B.R.A.H.M.S. AG, Hennigsdorf, Germany) as described previously [1].

Decline of eGFR Over Time and Incidence of CKD

Subjects were followed up until re-examination in 2007–2012 regarding decline of eGFR and new-onset of CKD, during a mean follow-up time of 16.6 ± 1.5 years. The change of eGFR was calculated by subtracting the follow-up values of eGFR from the baseline values (eGFR at baseline – eGFR at follow-up) and dividing it by the follow-up time in years (annual decline of eGFR in ml/min/1.73 m^2). Incident CKD was defined by the use of 3 different cutoff levels of eGFR. When defining the CKD end point as eGFR <60 ml/min/1.73 m^2 (CKD_60), subjects having prevalent CKD_60 at baseline were excluded. Similarly, in analyses of CKD end points defined as eGFR <45 (CKD_45) and 30 (CKD_30) ml/min/1.73 m^2, subjects with prevalent CKD_45 and CKD_30, respectively, were excluded. Our primary analysis was made using the MDRD formula (CKD_60_{MDRD}, CKD_45_{MDRD}

Table 1. Baseline characteristics

	Number of cases (n = 3,186)
Gender, men, n (%)	1,267 (39.8)
Age, years	56.4±5.7
Systolic blood pressure, mm Hg	139.0±18.1
Antihypertensive treatment, n (%)	476 (14.9)
Current smoking, n (%)	701 (22.0)
Diabetes mellitus, n (%)	187 (5.9)
Follow-up time, years	16.6±1.5
Copeptin, pmol/l[a]	4.98 (3.15–7.87)
GFR_MDRD_baseline, ml/min/1.73 m^2	74.7±14.6
GFR_CKD_EPI_baseline, ml/min/1.73 m^2	90.1±13.0 (n = 3,092)*

Mean ± SD (if not otherwise specified).
[a] Expressed as median (interquartile range).
* Discrepancy due to missing data.

Table 2. Baseline variables in relation to annual decline of eGFR

	MDRD		CKD-EPI	
	B (95% CI)	p value*	B (95% CI)	p value*
Copeptin vs. ΔeGFR	0.057 (0.022 to 0.093)	0.001	0.050 (0.022 to 0.077)	<0.001
eGFR_baseline vs. ΔeGFR	0.035 (0.032 to 0.037)	<0.001	0.030 (0.027 to 0.032)	<0.001
Smoking vs. ΔeGFR	0.040 (–0.042 to 0.123)	0.336	0.083 (0.018 to 0.148)	0.013
Diabetes vs. ΔeGFR	–0.005 (–0.152 to 0.141)	0.942	0.052 (–0.062 to 0.167)	0.371
Age (per year) vs. ΔeGFR	0.025 (0.019 to 0.031)	<0.001	0.034 (0.029 to 0.040)	<0.001
AHT vs. ΔeGFR	0.161 (0.061 to 0.260)	0.002	0.189 (0.110 to 0.267)	<0.001
SBP, mm Hg vs. ΔeGFR	0.004 (0.002 to 0.006)	<0.001	0.004 (0.002 to 0.006)	<0.001
Gender, men, n (%) vs. ΔeGFR	0.155 (0.079 to 0.230)	<0.001	0.020 (–0.040 to 0.079)	0.514

B = Beta coefficient; ΔGFR = change in GFR (ml/min/year); AHT = antihypertensive treatment; SBP = systolic blood pressure; copeptin is expressed per SD increment of log transformed values. Analysis adjusted for gender, age, smoking status, SBP, anti-hypertensive treatment, diabetes mellitus and baseline level of GFR.
* Significant p values.

and CKD_30_{MDRD}, respectively), but we also used the CKD-EPI formula of eGFR ($CKD\_60_{CKD-EPI}$, $CKD\_45_{CKD-EPI}$ and $CKD\_30_{CKD-EPI}$, respectively).

Statistical Methods

The distribution of copeptin was skewed to the right and therefore transformed using the natural logarithm. Copeptin was related to the decline in eGFR using multivariate adjusted linear regression models and to the risk of developing incident CKD by use of multivariate adjusted logistic regression. All models were adjusted for baseline level of eGFR, age, gender, systolic blood pressure, antihypertensive therapy, smoking, diabetes, LDL cholesterol, HDL cholesterol and follow-up time. Continuous variables are shown as means ± SD if normally distributed and as medians and interquartile range if skewed. Categorical variables are shown as numbers and percentages.

SPSS statistical software version 22.0 (SPSS Inc., Chicago, Ill., USA) was used for all calculations. A 2-sided p value of <0.05 was considered statistically significant.

Results

The baseline characteristics of the study are listed in table 1. Each SD increment of copeptin was associated with significantly greater annual decline of eGFR according to the MDRD formula (OR 0.057, 95% CI 0.022–0.093; p = 0.001) and according to the CKD-EPI formula (OR 0.050, 95% CI 0.022–0.077; p < 0.001; table 2). When

not adjusted for baseline eGFR, similar results were obtained according to the MDRD formula (OR 0.046, 95% CI 0.007–0.085; p = 0.020) as well as according to the CKD-EPI formula (OR 0.030, 95% CI 0.000–0.060; p < 0.051). Also as shown in table 3, each SD increment of copeptin independently predicted incident CKD_60_{MDRD} (OR 1.19, 95% CI 1.04–1.36; p = 0.010), CKD_45_{MDRD} (OR 1.33, 95% CI 1.04–1.71; p = 0.026) and CKD_30_{MDRD} (OR 3.69, 95% CI 1.41–9.66; p = 0.008). Furthermore, when sub-dividing the subjects into quintiles of copeptin, the highest quintile group (Q5) had a significantly increased risk of developing CKD_60_{MDRD} (OR 1.48, 95% CI 1.03–2.12; p = 0.032) compared to the reference quintile (Q1) with a significant trend over quintiles (p = 0.009). Similarly, there was a significant trend across quintiles of copeptin in relation to CKD_45_{MDRD} but no significant difference between the top and bottom quintiles. The quintile analysis of copeptin in relation to $CKD30_{MDRD}$ could not be assessed as there were no incident CKD_30_{MDRD} cases in the reference quintile (Q5).

When eGFR was estimated according to the CKD-EPI formula, copeptin did not significantly predict incident $CKD\_60_{CKD\text{-}EPI}$ (OR 1.09, 95% CI 0.99–1.19; p = 0.084); however, each SD increment of copeptin significantly and independently predicted incident $CKD\_45_{CKD\text{-}EPI}$ (OR 1.18, 95% CI 1.01–1.38; p = 0.043) and $CKD\_30_{CKD\text{-}EPI}$ (OR 1.88, 95% CI 1.13–3.12; p = 0.015; table 4). In analyses of copeptin quintiles, there was an increased risk of developing $CKD\_60_{CKD\text{-}EPI}$ in Q5 compared to the reference quintile (table 4; fig. 1), with a significant trend over quintiles (p = 0.009). Similarly, Q5 had a significantly increased risk of developing $CKD\_45_{CKD\text{-}EPI}$ compared to the reference quintile (table 4), with a significant trend over quintiles (p = 0.028). Furthermore, there was a significantly increased trend over quintiles in relation to incidence of $CKD\_30_{CKD\text{-}EPI}$ (p = 0.035), and the highest quintile group (Q5) had a borderline significantly increased risk of developing $CKD\_30_{CKD\text{-}EPI}$ compared to the reference quintile (table 4; online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000447522).

A sensitivity analysis, using the CKD-EPI formula, was performed near the studied threshold. Subjects with an eGFR >65 ml/min/1.73 m^2 at baseline were incorporated when studying eGFR <60, <45 and <30 ml/min/1.73 m^2 as end points (online suppl. table 2).

During a 16-year follow-up 1,172 (43.9%) subjects developed hypertension (diagnosed and treated) and 471 (15.7%) developed diabetes.

Table 3. Copeptin versus decline of eGFR calculated with MDRD

CKD_MDRD	Per 1 SD		p value**	Q1		Q2		Q3		Q4		Q5		p_{trend}**
	HR (95% CI)	n/n events*		HR (95% CI)	n/n events*	HR (95% CI)	n/n events*	HR (95% CI)	n/n events*	HR (95% CI)	n/n events*	HR (95% CI)	n/n events*	
<60 ml/min/1.73 m^2	1.19 (1.04–1.36)	2,795/434	0.010	1.0 (ref.)	559/77	0.99 (0.69–1.41)	559/73	1.04 (0.73–1.48)	559/81	1.33 (0.94–1.89)	559/95	1.98 (1.03–2.12)	559/108	0.009
<45 ml/min/1.73 m^2	1.33 (1.04–1.71)	3,167/127	0.026	1.0 (ref.)	633/22	0.91 (0.48–1.71)	634/20	0.98 (0.53–1.82)	633/22	1.50 (0.83–2.69)	632/30	1.57 (0.86–2.86)	635/33	0.047
<30 ml/min/1.73 m^2	3.69 (1.41–9.66)	3,184/12	0.008	1.0 (ref.)	637/0	NA	635/1	NA	638/3	NA	639/1	NA	635/7	NA

HR = Hazards ratio; Q1 = quintile 1; Q2 = quintile 2; Q3 = quintile 3; Q4 = quintile 4; Q5 = quintile 5; NA = not analyzed.
Analysis adjusted for gender, age, smoking status, systolic blood pressure, anti-hypertensive treatment, diabetes mellitus and baseline level of GFR.
* Refers to total number/number of incident CKD events.
** Significant p values.

Table 4. Copeptin versus decline of eGFR calculated with CKD-EPI formula

CKD_CKD-EPI	Per 1 SD		p value**	Q1		Q2		Q3		Q4		Q5		P_{trend}**
	HR (95% CI)	n/n events*		HR (95% CI)	n/n events*	HR (95% CI)	n/n events*	HR (95% CI)	n/n events*	HR (95% CI)	n/n events*	HR (95% CI)	n/n events*	
<60 ml/min/1.73 m^2	1.09 (0.99–1.19)	3,053/981	0.084	1.0 (ref.)	610/171	1.07 (0.81–1.41)	610/184	1.0 (0.76–1.33)	611/191	1.21 (0.91–1.61)	611/200	1.46 (1.09–2.00)	611/235	0.009
<45 ml/min/1.73 m^2	1.18 (1.01–1.38)	3,088/275	0.043	1.0 (ref.)	619/43	1.0 (0.62–1.60)	616/44	1.06 (0.67–1.67)	618/52	1.52 (0.97–2.39)	619/64	1.44 (0.91–2.28)	616/72	0.028
<30 ml/min/1.73 m^2	1.88 (1.13–3.12)	3,092/42	0.015	1.0 (ref.)	619/4	1.43 (0.38–5.36)	616/6	1.33 (0.36–4.94)	622/6	1.52 (0.42–5.49)	618/7	3.17 (1.00–10.1)	617/19	0.035

HR = Hazards ratio; Q1 = quintile 1; Q2 = quintile 2; Q3 = quintile 3; Q4 = quintile 4; Q5 = quintile 5.
Analysis adjusted for gender, age, smoking status, systolic blood pressure, anti-hypertensive treatment, diabetes mellitus and baseline level of GFR.
* Refers to total number/number of incident CKD events.
** Significant p values.

Fig. 1. Quintiles of copeptin versus annual decline of CKD calculated with CKD-EPI formula.

The number of subjects excluded at each analysis was 391 subjects if defined by CKD_60_{MDRD}, 19 if CKD_45_{MDRD}, 1 if CKD_30_{MDRD} and 39 if $CKD\_60_{CKD\text{-}EPI}$, 4 if $CKD\_45_{CKD\text{-}EPI}$ and 0 if $CKD\_30_{CKD\text{-}EPI}$.

Discussion

The key finding in our study is that in an unselected urban population, copeptin independently predicts development of new-onset CKD and a faster decline in eGFR over time. The risk of CKD_60_{MDRD} in the top quintile of copeptin was doubled compared to the reference quintile. Importantly, our results are in concordance with a recently published French community-based study, which also found high copeptin levels to be predictive of new onset CKD [17]. We thus replicate and extend those findings to be valid in a Northern European population.

Even though elevation of AVP, measured by copeptin, predicted CKD and decline of eGFR independent of all conventional risk factors in our general population, it is unknown if the associations that we found are causal. However in the literature, there is some evidence derived from animal studies and human intervention studies of patients suggesting that high AVP may in fact be causally related to impaired renal function. In animal studies, infusion of V2R agonists in rats has been linked to increased

mortality and proteinuria [7]. In addition, in rat model of type 1 diabetes, V2R antagonists have been shown to have beneficial effects on renal function [18]. Also, in Brattleboro rats lacking AVP expression that were only partially nephrectomized, CKD was less likely to develop [7]. Furthermore, in the same rat model, a 3-fold increase in water intake ameliorated proteinuria and glomerulosclerosis [19] indicating that water-induced suppression of AVP may be of renal protective importance. However, human subjects of the general population have not been examined in intervention studies. A study of tolvaptan blockade in patients with adult polycystic kidney disease [20] found that blockade of the V2R by administration of tolvaptan results in a slower progress of cyst growth, reduced decline in eGFR and reduced change in total kidney volume compared with the control group. Lastly, the significant annual decline in eGFR argues against that copeptin is solely a filtration marker since the relationship between copeptin versus eGFR is very similar when adjusted for baseline eGFR as well as without the adjustment. If anything, the adjusted relationship between copeptin and GFR decline is stronger than the crude one.

Based on the studies and findings mentioned, one can speculate that elevation of AVP plays a role in the development of CKD, presumably through an effect on the V2R. Thus, increased water intake or pharmacological vasopressin blockade are interesting candidates for preventing the decline of eGFR and development of CKD.

Elevation of copeptin has previously been associated with faster decline of eGFR in a high-risk population for CKD, that is, patients with type 2 diabetes [8]. Together with the recent data from a general French population [17], the current study extends the prior findings in patients with type 2 diabetes to be valid in a general population and include prediction of incident CKD. We suggest that copeptin may identify high-risk individuals for CKD beyond well-known risk groups such as diabetes patients. In such patients, screening for microalbuminuria and eGFR is obligatory and usually initiated early. The current findings, on the other hand, highlight the potential value of screening for elevated CKD risk in the general population, in the interest of targeted primary prevention offered to subjects of the general population at high risk of CKD. As we have previously shown that copeptin is related both to incidence of diabetes and to hypertension, we find it likely that part of the association between copeptin and CKD is mediated by new onset hypertension [4] and diabetes [3]. A more intense screening program with frequent measurements of renal function, and possibly more aggressive treatment of hypertension, may be motivated in a population with elevated values of copeptin, in order to prevent CKD.

As expected, the results regarding incident CKD differed depending on the cutoff level and formula used. The MDRD equation was developed using data from patients with an average measured eGFR of 40 ml/min/1.73 m^2 which makes this formula less suitable for individuals with a eGFR >60 ml/min/1.73 m^2 where it underestimates the true GFR. The formula was used in the calculations even though the population was healthy as it increases the accuracy of the results in those who developed CKD. On the other hand, the CKD-EPI equation was developed from a population that resembles the general population with a mean GFR of 68 ml/min/1.73 m^2. In any case, the continuous decline of eGFR was significantly higher for both MDRD and CKD-EPI equations in relation to baseline levels of copeptin. Quintile analyses showed similar trends for both eGFR formulas. We believe that part of the crude relationship between copeptin and eGFR is explained by the fact that copeptin is renally excreted. However, we adjusted for baseline level of eGFR in order to extract the proportion of variance in copeptin which explains decline in eGFR independently of baseline eGFR. We have emphasized that the known correlation between copeptin and eGFR is partially explained by copeptin being renally excreted.

There are some limitations of this study to acknowledge. First, the MDCS-CC had a participation rate of only 40% and can thus be assumed to consist of healthier individuals than the general population. In addition, only those who survived until the re-examination 16.6 years after the baseline examination had the follow-up determination of renal function performed and this likely further amplifies the healthy cohort effect. Secondly, details of cofounding variables such as dietary, salt and water intake are not available. Furthermore, we do not have data on albuminuria that is required for the diagnosis of CKD stages 1 and 2.

In conclusion, our data suggest that in a middle-aged population with eGFR >60 ml/min/1.73 m^2 at baseline, increased levels of copeptin independently predict decline in eGFR and a greater risk of reaching impaired eGFR de novo, as part of the definition of CKD (eGFR <60 ml/min/1.73 m^2). Furthermore, our data suggest that copeptin can be used to identify high-risk individuals for CKD development in order to offer early preventive strategies.

Acknowledgments

The study was funded by grants from the European Research Council (StG-282255), Swedish Medical Research Council, the Swedish Heart and Lung Foundation, the Medical Faculty of Lund University, Malmö University Hospital, the Albert Påhlsson Research Foundation, the Crafoord Foundation, the Ernhold Lundströms Research Foundation, the Region Skane, the Hulda and Conrad Mossfelt Foundation, the King Gustaf V and Queen Victoria Foundation, the Novo Nordisk Foundation, and the Wallenberg Foundation. Finally, thank to B.R.A.H.M.S. and Dade-Behring for their support of assay measurements.

Disclosure Statement

None.

References

1 Morgenthaler NG, et al: Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem 2006;52:112–119.
2 Baumann G, Dingman JF: Distribution, blood transport, and degradation of antidiuretic hormone in man. J Clin Invest 1976;57:1109–1116.
3 Enhörning S, et al: Copeptin, a marker of vasopressin, in abdominal obesity, diabetes and microalbuminuria: the prospective Malmö diet and cancer study cardiovascular cohort. Int J Obes (Lond) 2013;37:598–603.
4 Enhörning S, et al: Plasma copeptin, a unifying factor behind the metabolic syndrome. J Clin Endocrinol Metab 2011;96:E1065–E1072.
5 Enhörning S, et al: Plasma copeptin and the risk of diabetes mellitus. Circulation 2010;121:2102–2108.
6 Abbasi A, et al: Sex differences in the association between plasma copeptin and incident type 2 diabetes: the prevention of renal and vascular endstage disease (PREVEND) study. Diabetologia 2012;55:1963–1970.
7 Bouby N, Hassler C, Bankir L: Contribution of vasopressin to progression of chronic renal failure: study in Brattleboro rats. Life Sci 1999;65:991–1004.
8 Boertien WE, et al: Copeptin, a surrogate marker for arginine vasopressin, is associated with declining glomerular filtration in patients with diabetes mellitus (ZODIAC-33). Diabetologia 2013;56:1680–1688.
9 Velho G, et al: Plasma copeptin and renal outcomes in patients with type 2 diabetes and albuminuria. Diabetes Care 2013;36:3639–3645.
10 Riphagen IJ, 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;36:3201–3207.
11 Enhörning S, et al: Copeptin is an independent predictor of diabetic heart disease and death. Am Heart J 2015;169:549–556.e1.
12 Tasevska I, et al: Copeptin predicts coronary artery disease cardiovascular and total mortality. Heart 2016;102:127–132.
13 Zittema D, et al: Kidney function and plasma copeptin levels in healthy kidney donors and autosomal dominant polycystic kidney disease patients. Clin J Am Soc Nephrol 2014;9:1553–1562.
14 Rosvall M, et al: Incident coronary events and case fatality in relation to common carotid intima-media thickness. J Intern Med 2005;257:430–437.
15 Levey AS, et al: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. Ann Intern Med 1999;130:461–470.
16 Inker LA, et al: Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–29.
17 Roussel R, et al: Plasma copeptin and decline in renal function in a cohort from the community: the prospective D.E.S.I.R. study. Am J Nephrol 2015;42:107–114.
18 Bardoux P, et al: Diabetes-induced albuminuria: role of antidiuretic hormone as revealed by chronic V2 receptor antagonism in rats. Nephrol Dial Transplant 2003;18:1755–1763.
19 Bouby N, et al: Effect of water intake on the progression of chronic renal failure in the 5/6 nephrectomized rat. Am J Physiol 1990;258(4 pt 2):F973–F979.
20 Torres VE, et al: Effect of tolvaptan in autosomal dominant polycystic kidney disease by CKD stage: results from the TEMPO 3:4 trial. Clin J Am Soc Nephrol 2016;11:803–811.