Diagnostic Accuracy of Copeptin in the Differential Diagnosis of the Polyuria-polydipsia Syndrome: A Prospective Multicenter Study

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Context: The polyuria-polydipsia syndrome comprises primary polydipsia (PP) and central and nephrogenic diabetes insipidus (DI). Correctly discriminating these entities is mandatory, given that inadequate treatment causes serious complications. The diagnostic “gold standard” is the water deprivation test with assessment of arginine vasopressin (AVP) activity. However, test interpretation and AVP measurement are challenging.

Objective: The objective was to evaluate the accuracy of copeptin, a stable peptide stoichiometrically cosecreted with AVP, in the differential diagnosis of polyuria-polydipsia syndrome.

Design, Setting, and Patients: This was a prospective multicenter observational cohort study from four Swiss or German tertiary referral centers of adults >18 years old with the history of polyuria and polydipsia.

Measurements: A standardized combined water deprivation/3% saline infusion test was performed and terminated when serum sodium exceeded 147 mmol/L. Circulating copeptin and AVP levels were measured regularly throughout the test. Final diagnosis was based on the water deprivation/saline infusion test results, clinical information, and the treatment response.

Results: Fifty-five patients were enrolled (11 with complete central DI, 16 with partial central DI, 18 with PP, and 10 with nephrogenic DI). Without prior thirsting, a single baseline copeptin level >21.4 pmol/L differentiated nephrogenic DI from other etiologies with a 100% sensitivity and specificity, rendering a water deprivation testing unnecessary in such cases. A stimulated copeptin >4.9 pmol/L (at sodium levels >147 mmol/L) differentiated between patients with PP and patients with partial central DI with a 94.0% specificity and a 94.4% sensitivity. A stimulated AVP >1.8 pg/mL differentiated between the same categories with a 93.0% specificity and a 83.0% sensitivity.

Limitation: This study was limited by incorporation bias from including AVP levels as a diagnostic criterion.

Conclusion: Copeptin is a promising new tool in the differential diagnosis of the polyuria-polydipsia syndrome, and a valid surrogate marker for AVP.

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Abbreviations: AUC, under the curve; AVP, arginine vasopressin; CI, confidence interval; DI, diabetes insipidus; PP, primary polydipsia.
The polyuria-polydipsia syndrome comprises three major entities: central (complete or partial) diabetes insipidus (DI), nephrogenic (complete or partial) DI, and primary polydipsia (PP). Differentiating these entities is important, given that inadequate treatment may lead to serious complications, eg, profound hyponatremia. The diagnostic “gold standard” consists of a water deprivation test, after which urine osmolality should provide the correct diagnosis. However, test interpretation is often challenging, especially in distinguishing PP from partial forms of DI, given that the kidney’s maximum concentrating ability is often impaired due to a washout of the renal salt gradient (1). Accordingly, in a recent study, the water deprivation test led to a correct diagnosis in only 70% of patients, including only 41% of patients with PP (2).

Direct measurement of plasma vasopressin (AVP) before and after a thirsting period has been recommended for better patient classification (3, 4). Although direct AVP measurement led to a significantly better patient classification compared with urine osmolality measurement alone (4), this concept has not become accepted as the diagnostic standard due to several shortcomings. First, the normal range of plasma AVP in relation to plasma osmolality was originally established by studying a very small group (5), whereas a recent larger study found a less close association between the two parameters (2). Second, reliable plasma AVP measurement is cumbersome due to multiple preanalytical (6–10) and technical difficulties (6, 8, 10). In contrast, copeptin, the C-terminal glycoprotein moiety of pro-AVP, is a stable surrogate marker of AVP secretion. Copeptin recently has been suggested to improve the differential diagnosis of DI (2), to mirror water deprivation and excess in healthy subjects (11), and to assess posterior pituitary function (12).

The present study sought to prospectively investigate the performance of copeptin at baseline and after osmotic stimulation in the differential diagnosis of the entire spectrum of the polyuria-polydipsia syndrome.

Materials and Methods

Study cohort

In this prospective multicenter study, all adults referred to the Endocrine Units of the University Hospitals Basel, Aarau, and Bern, Switzerland, and Würzburg, Germany, from October 2008 to August 2012 for diagnostic evaluation of the polyuria-polydipsia syndrome were screened for eligibility. Inclusion criteria were greater than 18 years of age and history of polyuria (>40 mL/kg/d) and polydipsia. Exclusion criteria were osmotic diuresis due to diabetes mellitus or hypercalcemia, pregnancy, uncorrected thyroid or adrenal insufficiency, and heart failure. The local ethical committees approved the study. Written informed consent was obtained from all patients. The study was preregistered on ClinicalTrials.gov (NCT00757276).

Combined water deprivation/saline infusion test

All patients underwent a standardized water deprivation test starting at 0800 h, without prior fluid restriction, according to the Robertson et al (4, 13) protocol, as long as baseline plasma sodium did not exceed 147 mmol/L. The test was stopped when plasma sodium exceeded 147 mmol/L. At baseline and hourly during the test, blood pressure, pulse rate, and weight were monitored. Blood was sampled for measurement of plasma sodium, osmolality, AVP, and copeptin, and urine was sampled for osmolality determination.

If plasma sodium levels increased greater than 147 mmol/L or were greater than 147 mmol/L at baseline, and urine osmolality remained less than 300 mmol/kg H2O, the test was discontinued and a desmopressin challenge (2 μg i.v.; Ferring Pharmaceuticals, Baar, Switzerland) was performed. Urine osmolality was measured before and 1 hour after desmopressin injection. If plasma sodium did not exceed 147 mmol/L by thirsting alone by 1300 h, patients received a 3% saline infusion at 0.1 mL/kg body weight/min and blood was sampled every 30 minutes thereafter for measurement of plasma sodium, osmolality, AVP, and copeptin. The test was terminated when plasma sodium exceeded 147 mmol/L.

Interpretation of the combined water deprivation/saline infusion test

If upon thirsting alone, plasma sodium levels increased to greater than 147 mmol/L and urine osmolality remained less than 300 mmol/kg H2O, complete DI was diagnosed. If urine osmolality increased greater than 50% in response to desmopressin, complete central DI was diagnosed, whereas a less than 50% increase diagnosed complete nephrogenic DI. If urine osmolality increased to greater than 300 mmol/kg H2O before plasma sodium exceeded 147 mmol/L, partial central or partial nephrogenic DI or PP was diagnosed. In these cases, patients were further classified based on AVP levels in relation to plasma osmolality levels (4, 5). If baseline plasma AVP levels were greater than 2 pg/mL, whereas peak AVP levels (at plasma sodium >147 mmol/L during fluid deprivation and hypertonic saline infusion) were normal or high in relation to the concurrent plasma osmolality (4, 5), partial nephrogenic DI was diagnosed. If baseline plasma AVP levels were less than 2 pg/mL and peak AVP levels were below normal in relation to the concurrent plasma osmolality, partial central DI was diagnosed. If baseline plasma AVP levels were less than 2 pg/mL and peak AVP levels were normal in relation to the concurrent plasma osmolality, PP was diagnosed.

Final diagnosis

Because no established diagnostic “gold standard” exists, the final diagnosis was made after careful, comprehensive evaluation by two independent experts in the field, blinded to copeptin levels, according to the three diagnostic components outlined below (2, 14). The final diagnosis was based on 1) the results of the combined water deprivation/saline infusion test (including AVP levels) as described above, 2) additional features such as the patient’s history including psychiatric disease, head trauma or surgery, family history, symptom onset, consistency of fluid intake, nocturia, and fluid preferences (14), as well as diagnostic findings (including anterior pituitary function tests, cranial magnetic resonance imaging, evidence of autoimmune/inflammatory
Discrete variables are expressed as numbers (percentages) and continuous variables as medians (interquartile range). The same procedure was followed for stimulated and delta copeptin levels. Delta copeptin was calculated as stimulated copeptin at a plasma sodium level greater than 147 mmol/L — baseline copeptin, and delta AVP was calculated as stimulated AVP at a plasma sodium level greater than 147 mmol/L — baseline AVP.

Testing was two tailed, and $P < .05$ was considered statistically significant. For statistical analysis, we used Stata 12.0 (StataCorp LLP, College Station, TX).

Results

Baseline characteristics

Fifty-five patients with the polyuria-polydipsia syndrome were included in the study. Baseline characteristics are shown in Table 1. Patients in the complete nephrogenic DI group were older, had a higher plasma osmolality, higher plasma sodium levels, and a higher lithium intake ($P = .004$, $P = .0008$ and $P = .0057$) whereas 24 hours fluid intake was higher in complete central DI patients ($P = .0037$). Otherwise, there were no statistically significant differences in the baseline characteristics between the entities of the polyuria-polydipsia syndromes.

Baseline AVP and copeptin levels

Baseline AVP levels ranged from 3.0–16.7 pg/mL in nephrogenic DI patients (complete, 3.0–16.7 pg/mL; partial, 4.2–12.1 pg/mL), from 0.5–2.4 pg/mL in central DI patients (complete, 0.5–1.4 pg/mL; partial, <0.5–2.4 pg/mL), and from 0.5–2.7 pg/mL in PP patients (Figure 1A). Baseline copeptin levels ranged from 21.4–117.0 pmol/L in patients with nephrogenic DI (complete, 38.7–117.0 pmol/L; partial, 21.4–26.6 pmol/L), from 0.7–5.1 pmol/L in patients with central DI (complete, 0.7–3.4 pmol/L; partial, 0.9–5.1 pmol/L), and from 0.9–13.5 pmol/L in patients with PP (Figure 1B).

<table>
<thead>
<tr>
<th>Table 1. Baseline Patient Characteristics by Polyuria-Polydipsia Syndrome Entity (n = 55)</th>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Age, yr, median (IQR)</td>
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<tr>
<td>Sex, F/M (% F)</td>
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<tr>
<td>BMI, kg/m², median (IQR)</td>
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<tr>
<td>Fluid intake, L, median (IQR)</td>
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<tr>
<td>Nighttime fluid intake, yes/no (% yes)</td>
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<tr>
<td>Plasma sodium, mmol/L, median (IQR)</td>
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<tr>
<td>Plasma osmolality, mmol/kg H2O, median (IQR)</td>
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<tr>
<td>Hypovolemic/euvolemic/hypervolemic status (% euvolemic)</td>
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<tr>
<td>DBP, mm Hg, median (IQR)</td>
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Abbreviations: BMI, body-mass index; BW, body weight; DI, diabetes insipidus; DBP, diastolic blood pressure; F, female; IQR, interquartile range; M, male; SBP, systolic blood pressure.

Discrete variables are expressed as numbers (percentages) and continuous variables as medians (IQR).
Osmotically stimulated AVP and copeptin during the combined water deprivation/saline infusion test

Osmotically stimulated plasma AVP levels (at a sodium concentration of greater than 147 mmol/L during the combined water deprivation/saline infusion test) ranged from 0.5–1.2 pg/mL and 0.8–1.8 pg/mL in patients with complete and partial central DI, and from 0.7–12.2 pg/mL in patients with PP (Figure 2A). Stimulated copeptin levels ranged from 0.7–3.3 pmol/L and 0.7–7.0 pmol/L, respectively, in patients with complete and partial central DI, and from 3.7–24.4 pmol/L in patients with PP (Figure 2B). In five of six patients with complete nephrogenic DI, plasma sodium levels were already greater than 147 mmol/L at baseline and consequently, according to the protocol, no stimulation test was performed. Therefore, copeptin and AVP levels in these patients did not differ from baseline levels. In patients with partial nephrogenic DI, stimulated AVP levels ranged from 2.5–7.7 pg/mL, and stimulated copeptin levels ranged from 19.3–39.9 pmol/L.

Correlation of copeptin and AVP levels

Baseline and stimulated copeptin correlated with corresponding AVP plasma levels (r = 0.68, P < .001; r = 0.81, P < .001, respectively). Delta copeptin (ie, stimulated copeptin–baseline copeptin) correlated with delta AVP (r = 0.70, P < .001).

Baseline AVP and copeptin levels in differential diagnosis of the polyuria-polydipsia syndrome

Without prior thirsting, an AVP level of at least 3.0 pg/mL or a copeptin level of at least 21.4 pmol/L at baseline (Figure 1, A and B) differentiated all patients with nephrogenic DI from patients with other diagnoses with 100% sensitivity and specificity (respective AUCs [95% confidence intervals; CIs] 1.0, [1.0–1.0] and 1.0, [1.0–1.0], comparison of AUCs, P = not statistically significant [n.s.]). A baseline copeptin level of at least 2.9 pmol/L differentiated between patients with central DI (complete and partial) and other diagnoses with 82% sensitivity and 78% specificity (AUC [95% CI], 0.81 [0.68–0.93]). In comparison, a baseline AVP of at least 1.8 pg/mL differentiated between these diagnoses with 54% sensitivity and 89% specificity (AUC [95% CI], 0.69 [0.55–0.84]; comparison of AUCs, P = n.s.).

Osmotically stimulated AVP and copeptin levels in differential diagnosis of the polyuria-polydipsia syndrome

An osmotically stimulated AVP level of at least 1.8 pg/mL had 83% sensitivity and 93% specificity (AUC [95% CI], 0.89 [0.76–1.00]), whereas a stimulated copeptin level of at least 4.9 pmol/L had 94% sensitivity and specificity (AUC [95% CI], 0.98 [0.95–1.00]) to differentiate between PP and partial central DI (comparison of AUCs, P = n.s.). Regarding the discrimination of PP vs
combined water deprivation/saline infusion test. Patients (96%) through copeptin measurement and the
Hence, a definite diagnosis could be established in 53/55
with PP, and in 10/10 patients with nephrogenic DI.

In 15/16 patients with partial central DI, in 18/18 patients
with PP, and in 10/10 patients with nephrogenic DI.
Hence, a definite diagnosis could be established in 53/55
patients (96%) through copeptin measurement and the
combined water deprivation/saline infusion test.

Discussion
The results of this prospective international multicenter
study show that plasma copeptin is a reliable marker to
discriminate between different entities of the polyuria-
polydipsia syndrome and correlates well with AVP plasma
levels. The study had the following main findings. First,
a single baseline copeptin measurement without prior fluid
restriction reliably discriminates patients with nephro-
genic DI from patients with all other entities of the poly-
uria-polydipsia syndrome, rendering a water deprivation
test unnecessary in the former subgroup. Second, a base-
line copeptin measurement allowed a good but not un-
equivocal identification of patients with complete central
DI. Third, osmotically stimulated copeptin values differ-
etiated between PP and partial central DI with 94% sen-
tivity and specificity, which was even higher when pa-
tients with complete central DI were included in the
analysis. Given that treatment does not differ in patients
with partial vs complete central DI, a strict differentiation
between these two entities is generally of minor clinical
relevance. Overall, with the help of copeptin, a definite
diagnosis was achieved in 96% of patients.

Our results show that the performance of copeptin and
AVP are quite similar. The major advantage of using co-
peptin instead of AVP in the diagnostic workup of patients
with the polyuria-polydipsia syndrome is, that copeptin is
more reliable and much easier to measure in clinical rou-
tine due to a standardized, fast assay that can be used all
during the world with only a small interassay variability and
due to very little preanalytical challenges. To reduce po-

Table 2. Plasma Copeptin and AVP for the Discrimination of Polyuria-Polydipsia Syndromes: AUCs and Proposed
diagnostic cutoffs with sensitivity and specificity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nephrogenic DI Versus Other Polyuria-Polydipsia Syndrome Diagnoses, AUC (95% CI)</th>
<th>Other Polyuria-Polydipsia Syndrome Diagnoses, AUC (95% CI)</th>
<th>Primary Polydipsia Versus Partial Central DI, AUC (95% CI)</th>
<th>Primary Polydipsia Versus Central (Partial and Complete) DI, AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline plasma copeptin cutoffs, pmol/L (sensitivity/specifity, %)</td>
<td>1.00 (1.00–1.00)</td>
<td>0.74 (0.59–0.88) Cutoff: ≥214 (100%/100%)</td>
<td>0.68 (0.49–0.88) P = n.s.</td>
<td>0.70 (0.53–0.88) Cutoff: ≥0.9 (100%/4%)</td>
</tr>
<tr>
<td>Stimulated plasma copeptin cutoffs, pmol/L (sensitivity/specifity, %)</td>
<td>0.90 (0.81–0.98) Cutoff: ≥2.6 (89%/82%)</td>
<td>0.80 (0.94–1.00) Cutoff: ≥3.7 (100%/81%)</td>
<td>0.90 (0.80–1.00) Cutoff: ≥3.7 (100%/89%)</td>
<td>0.90 (0.80–1.00) Cutoff: ≥3.7 (100%/89%)</td>
</tr>
<tr>
<td>Baseline plasma AVP cutoffs, pg/mL (sensitivity/specifity, %)</td>
<td>0.66 (0.51–0.80) Cutoff: ≥0.6 (99%/99%)</td>
<td>0.50 (0.31–0.71)</td>
<td>0.50 (0.35–0.72)</td>
<td>0.50 (0.35–0.72)</td>
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</table>

Abbreviation: n.s. = not statistically significant (P > .05).

Potential diagnostic cutoffs for baseline and osmotically stimulated (ie, at a plasma sodium level >147 mmol/L) AVP are given with their respective sensitivity and specificity in parentheses. Proposed clinically useful cutoffs for copeptin and AVP for each differential diagnoses are shown in bold.
tential variability in AVP-measurement, due to the known preanalytical problems as observed in other studies (2), in our study AVP samples have been obtained under standardized optimized conditions and AVP was measured in Chicago using the methodology of Robertson et al (4).

The indirect water deprivation test has been the diagnostic “gold standard” to differentiate between PP and partial central DI. However, in a recent study, this approach provided a classification agreeing with the final diagnosis in only 41% of patients (2). Moreover, in that study, direct AVP measurement combined with the water deprivation test correctly diagnosed only 40% of patients with PP who attained a serum osmolality greater than 290 mmol/kg H2O after 16 hours (2). In our study, direct AVP measurement according to the protocol of Robertson et al (4, 5) led to a definite diagnosis of PP in only 44% of patients with this entity, although high plasma sodium (>147 mmol/L) or plasma osmolality (>295 mmol/kg H2O) levels, or both, were obtained in all patients. Nine of 18 patients with PP were falsely diagnosed with partial central DI and one of 18 patients with PP was incorrectly diagnosed with partial nephrogenic DI. The poor performance of AVP in differentiating PP may have different reasons. The relationship defined for AVP and plasma osmolality that serves as a diagnostic tool in the combined water deprivation/saline infusion test is based on a small number (n = 11) of individuals in the original publication (5). Furthermore, and as noted previously (2), the original publications (5, 17, 18) did not describe how the AVP reference range in relation to plasma sodium was established. In addition, reliable AVP measurement is cumbersome due to preanalytical difficulties, given that the mature hormone is highly unstable (6), largely attached to platelets (7), and rapidly cleared from plasma (6, 8–10). By contrast, copeptin, which is cosecreted stoichiometrically with AVP (11, 12, 19), is more stable, and can be easily measured in serum or plasma (6, 15).

Our findings support and expand on earlier findings by Fenske et al (2) concerning the diagnostic utility of copeptin in the polyuria-polydipsia syndrome. However, some of our results also differ. First, the diagnostic accuracy of stimulated plasma copeptin levels to differentiate between patients with PP vs partial central DI was higher in our study. This observation might be explained by the fact that in the Fenske study, almost half of the patients had an insufficient increase in serum osmolality at the end of the water deprivation test and therefore had a limited stimulus for copeptin and AVP secretion. This observation highlights the importance of a sufficient increase in serum osmolality and sodium levels, which in our study, was achieved by administration of a hypertonic saline infusion subsequent to the water deprivation test if necessary. Second, a single baseline copeptin measurement could not unequivocally diagnose complete central DI in our study, most probably due to differences in protocols, given that baseline copeptin values in the Fenske study were obtained after overnight thirsting, whereas in our study, baseline copeptin values were measured at 0800 h with prior ad libitum fluid intake.

The strengths of our study include the evaluation of the diagnostic accuracy of copeptin in patients with all entities of the polyuria-polydipsia syndrome, encompassing a relevant number of patients with nephrogenic DI, and a test protocol ensuring a significant osmotic stimulus in all patients. However, our study had several limitations. First, the final diagnosis, based on the combined water deprivation and saline infusion test with AVP measurements, clinical features, and treatment response, was not standardized. However, because no validated “gold standard” is available, every diagnostic study struggles with this limitation. Our diagnostic approach has been assessed previously and also is commonly used in clinical routine (2). Second, by evaluating the diagnostic accuracy of AVP, we introduced an incorporation bias, given that AVP levels contributed to our final diagnosis. However, this factor may have led only to a bias toward the null hypothesis for the performance of copeptin (underestimation of diagnostic accuracy) in comparison with AVP (overestimation of diagnostic performance). Third, copeptin cutoffs were generated in the same cohort used to evaluate its diagnostic accuracy. Overall, the proposed copeptin cutoffs must be validated prospectively in multicenter studies including sufficiently high numbers of patients of all entities of the polyuria-polydipsia syndrome.

In summary, measurement of baseline copeptin levels without prior fluid restriction allows unequivocal diagnosis of patients with nephrogenic DI. Measurement of circulating copeptin levels upon a sufficient osmotic stimulus provides a new tool to discriminate between complete and partial central DI vs PP. Copeptin therefore improves and simplifies differential diagnosis in the polyuria-polydipsia syndrome.

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funding source had any other involvement in the collection, analysis, or interpretation of the data or the decision to approve publication of the finished manuscript. The principal investigators had complete and final control of the study design and conduct, database, statistical analysis, publication decisions, and manuscript content.

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Author Contributions: K.T. and M.K. were involved in the study design, study coordination, recruitment of patients, and statistical analysis, and they drafted the manuscript. W.F. recruited patients and drafted the manuscript. F.K., N.F., and B.A. were involved in the study coordination and recruited patients. P.K., B.A.L., C.S., J.R., and B.M. were involved in study coordination, gave staff support, and drafted the manuscript. M.C.-C. designed and coordinated the study, drafted the manuscript, and gave financial and staff support. All authors read and approved the final manuscript. Robert Marlowe edited the manuscript.

This study was registered in ClinicalTrials.gov as trial number NCT00757276.

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