Copeptin in the Differential Diagnosis of Hyponatremia

Wiebke Fenske, Stefan Störk, Anne Blechschmidt, Sebastian G. K. Maier, Nils G. Morgenthaler, and Bruno Allolio

Department of Endocrinology and Diabetes Unit (W.F., A.B., B.A.), Cardiology Unit (S.S.), Division of Intensive Care Medicine (S.G.K.M.), and Department of Medicine I, University of Würzburg, 97080 Würzburg, Germany; and Research Department (N.G.M.), B.R.A.H.M.S. AG, D-16761 Hennigsdorf/Berlin, Germany

Background: Treatment of patients with hyponatremia varies widely; thus, convenient diagnostic parameters are needed to guide the correct treatment strategy. This study was designed to evaluate the diagnostic potential of copeptin, the C-terminal part of provasopressin, as a new marker in the differential diagnosis of hyponatremia.

Methods: In this prospective observational study, 106 consecutive hyponatremic patients were classified based on their history, clinical evaluation, and laboratory tests. In patients and 32 healthy control subjects, plasma copeptin concentration and standard biochemical parameters were tested for their utility of diagnosing the syndrome of inappropriate antidiuresis (SIAD).

Results: Four patients (4%) were diagnosed as primary polydipsia, nine (8%) as diuretic-induced hyponatremia, 42 (40%) as SIAD, 29 (27%) as hypovolemic hyponatremia, and 22 patients (21%) as hypervolemic hyponatremia. In controls, a close correlation between plasma copeptin and serum sodium ($r^2 = 0.62$, $P < 0.001$) or urine osmolality ($r^2 = 0.39$, $P = 0.001$) was observed. Plasma copeptin levels were significantly higher in patients with hypo- and hypervolemic hyponatremia compared with SIAD ($P < 0.005$, respectively) and primary polydipsia ($P < 0.001$). The copeptin to U-Na ratio differentiated accurately between volume-depleted and normovolemic disorders (area under the receiver-operating characteristic curve 0.88, 95% confidence interval 0.81–0.95; $P < 0.001$), resulting in a sensitivity and specificity of 85 and 87% if a cutoff value of 30 pmol/mmol was used. The combined information of plasma copeptin less than 3 pmol/liter and urine osmolality less than 200 mOsm/kg ensured primary polydipsia in 100% of suspected patients.

Conclusion: Copeptin measurement reliably identifies patients with primary polydipsia but has limited utility in the differential diagnosis of other hyponatremic disorders. In contrast, the copeptin to U-Na ratio is superior to the reference standard in discriminating volume-depleted from normovolemic hyponatremic disorders. (***J Clin Endocrinol Metab*** **94: 123–129, 2009)**

Hyponatremia is the most common fluid and electrolyte disturbance occurring in a broad spectrum of patients from the asymptomatic to the critically ill (1). The prevalence of hyponatremia, defined as serum sodium less than 135 mmol/liter, may be as high as 15–30% in hospitalized patients (2). Because of the variety of disorders causing hyponatremia involving different, in part unknown, pathomechanisms, the diagnostic approach to hyponatremia is often complex and time consuming and the underlying cause of hyponatremia, and the resulting therapeutic decisions remain frequently ill defined with potential deleterious sequelae (3, 4). Therefore, readily available and reliable parameters for the differential diagnosis of hyponatremia are needed to facilitate a timely therapeutic strategy.

From a pathophysiological point of view, plasma arginine vasopressin (AVP) is a promising marker for several reasons. Because nonosmotic or osmotically inappropriate AVP secretion is the predominant mechanism in most hyponatremic disorders (5), abnormally elevated plasma AVP levels are detected in the

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Abbreviations: AQP2, Aquaporine-2; AVP, arginine vasopressin; CI, confidence interval; copeptin to U-Na (ratio), urinary sodium excretion to plasma copeptin ratio; SIAD, syndrome of inappropriate antidiuresis; V2R, vasopressin-2 receptor.

majority of underlying pathophysiologies (6, 7). In contrast to commonly used indirect parameters of AVP release as urine osmolality and solute-free water clearance, AVP is not limited by a slow response time, varies over a broad range of concentrations, is unaffected by glomerular filtration, and is not sensitive to renal function. Therefore, AVP measurement could be used to detect large or rapid changes in plasma AVP to differentiate AVP-dependent from AVP-independent causes of urinary concentration (8) and to detect hyponatremic disorders with suppressed AVP levels (9). Furthermore, the measurement of plasma AVP together with a volume-dependent parameter holds the potential to differentiate between disorders with primary AVP release, as the syndrome of inappropriate antidiuresis (SIAD), and disorders with AVP secretion secondary to a hemodynamic stimulus, as congestive heart failure or sodium depletion.

However, plasma AVP measurement has not become part of the routine diagnostic approach to hyponatremia, in particular because of significant preanalytical and analytical problems with AVP determination (10, 11). Due to its instability (12), low plasma concentration, and considerable association with platelets (13), measurement of circulating AVP is technically demanding, and reliable assays for AVP are not readily available. In search of a more robust way to quantify AVP release, copeptin has been proposed as a potential alternative for the direct measurement of AVP concentration. Copeptin, a 39-amino acid glycopeptide of unknown function, is derived from the same precursor peptide as AVP and is released in equimolar amounts together with AVP (14, 15). In contrast to AVP, copeptin is highly stable *ex vivo* and has recently been shown to be a reliable surrogate of plasma AVP in critically ill patients (11, 16). Furthermore, it also reflects changes in volume regulation and osmoregulation in healthy subjects (17). Accordingly, evaluation of plasma copeptin concentration in patients with hyponatremia has been suggested to circumvent the numerous technical drawbacks of AVP measurement (11, 17, 18). However, no studies have investigated the value of copeptin in hyponatremia so far.

Therefore, the current study aimed to evaluate the diagnostic potential of copeptin as a surrogate of AVP secretion in hyponatremic patients. In addition, we analyzed the diagnostic utility of the urinary sodium excretion to plasma copeptin ratio (copeptin to U-Na) ratio in discerning different causes of hyponatremia.

Patients and Methods

Study design and population

Between March and November 2007, all patients presenting at the Medical Department of the University of Würzburg with hypoosmolar hyponatremia at admission were consecutively screened for the study. Eligibility criteria for the present study were serum sodium less than 130 mmol/liter, serum osmolality less than 280 mOsm/kg H_2O on admission, and age older than 18 yr. Patients whose previous pharmacotherapy could not be reliably specified and patients with impaired renal function (serum creatinine $>$ 3.0 mg/dl) were not eligible. Furthermore, serum, plasma, and urine samples were collected from 32 healthy individuals, aged older than 18 yr, without evidence of acute disease or a history of chronic illness. The study was approved by the Ethics Committee of the University of Würzburg (no. 33/07), and written informed consent was obtained from all subjects before participation.

The determination of the underlying cause of hyponatremia was accomplished by a standardized structured diagnostic approach that was based on history, physical examination, laboratory tests, and follow-up. A detailed medical history was obtained emphasizing reason for admission, pharmacotherapy, diet, and quantity and type of oral and iv fluids received the day before inclusion. All fluids taken orally and iv and all renal fluid losses were recorded for 24 h. Each patient underwent a standardized clinical and biochemical evaluation. The extracellular fluid volume status was assessed by one of the authors (W.F.) as described by Chung *et al.* (4) and McGee *et al.* (19) with special attention to orthostatic changes in pulse rate and blood pressure. Orthostatic hypotension and orthostatic change in pulse rate were defined as reduction in systolic blood pressure of 20 mm Hg or greater and the increase in pulse rate of 30% or greater after 1 min in the upright body position compared with the supine position, respectively.

Laboratory assessment

The biochemical evaluation was performed in samples obtained before any therapeutic intervention and included the following parameters: serum sodium, potassium, chloride, creatinine, urea, uric acid, glucose, total protein, albumin, triglycerides, osmolality, red and white cell blood count, cortisol, ACTH, plasma renin, aldosterone, and TSH. Venous samples for the measurement of plasma copeptin were taken into EDTA tubes during morning hours in fasting patients after resting in supine position for at least 30 min. A urine specimen was collected and sodium, potassium, chloride, osmolality, creatinine, urea, uric acid, glucose, and protein were measured. The fractional excretion of filtered sodium, urea, and uric acid was estimated by the formula: fractional excretion$_x$ = ($U_x \times P_{Creatinin}/U_{Creatinin} \times P_x$) $\times$ 100, where U = urinary, P = plasma, x = substance to be calculated.

Routine laboratory measurements were done by automated chemical analyses in the Central Core Laboratory of the University Hospital Würzburg. Specifically, urine and serum samples were analyzed using ion-sensitive electrodes for sodium, potassium, and chloride. The glutamate dehydrogenase method was used for the determination of urea levels; a modification of the Jaffe method for creatinine measurement and osmolality was measured directly via determination of freezing point depression. The hexokinase and uricase methods were used for the determination of glucose and uric acid levels. Measurement of cortisol, ACTH, and TSH was assessed by using the appropriate assay for the autochemiluminescence system IMMULITE 2000 (Siemens, Medical Solution, Diagnostic GmbH, Bad Nauheim, Germany). Measurements of plasma aldosterone (Diagnostic Products, Los Angeles, CA) and renin (Cis-Bio International, Marcoule, France) were performed by RIA using commercially available assays. Copeptin was measured in a blinded fashion in a single batch with a commercial sandwich immunoluminometric assay (LUMItest CT-proAVP; B.R.A.M.H.S. AG, Hennigsdorf/Berlin, Germany) as described previously (10, 16). Since this initial publication, the assay was modified as follows: the capture antibody was replaced by a murine monoclonal antibody directed to amino acids 137-144 (GPAGAL) of proAVP. This modification improved the sensitivity of the assay. The lower detection limit was 0.4 pmol/liter and the functional assay sensitivity ($<$20% interassay coefficient of variation) was less than 1 pmol/liter.

Diagnostic criteria and classification

In all patients the cause of hyponatremia was determined independently by two investigators (W.F. and B.A.). In case of discrepancies, the final diagnosis was jointly determined in retrospect, with the knowledge of the complete diagnostic work-up, including imaging and histopathology results, and, if needed, the therapeutic response to water restriction or saline infusion. Results of plasma copeptin measurements were not taken into account.

All patients were classified into five categories, based on the principal causes of hyponatremia as described previously by Kumar and Berl (1):

1) the rare normovolemic disorders with hyponatremia due to excessive water intake in disturbed free water excretion (*e.g.* primary polydipsia) (3), 2) hypovolemic or euvolemic disorders due to renal sodium loss (*e.g.* diuretic induced), 3) normovolemic disorders fulfilling the criteria for SIAD as described by Schwartz *et al.* (20), hypovolemic disorders due to extrarenal sodium loss (*e.g.* vomiting, diarrhea, malnutrition), and 5) hypervolemic disorders with an excess of total body sodium and a larger excess of total body water due to nonosmotic AVP secretion (*e.g.* cardiac failure, liver cirrhosis).

In case of diagnostic uncertainty, the discrimination between SIAD and hypovolemic hyponatremia was based on a 24-h test infusion of 2 liters of isotonic saline. Patients with an initial FE-Na less than 0.5% and a ΔFE-Na (*i.e.* difference in FE-Na before and after saline infusion) less than 0.5%, were classified as sodium depleted; otherwise, a diagnosis of SIAD was accepted.

Mutation analysis

Genomic DNA from three patients with SIAD and undetectable copeptin levels was isolated from whole blood with the use of the Puregene blood kit (Gentra Systems, Minneapolis, MN). The entire coding region of the V2R and AQP2 gene was amplified as described previously (21). The resulting amplicons were sequenced with multiple forward and reverse primers with the use of Big Dye (version 3.1, Stratagene Inc., La Jolla, CA) sequencing chemistry and an ABI prism sequencer (Applied Biosystems, Inc., Foster City, CA) according to the manufacturer's protocols. SeqScape software was used to assemble the sequence data and compare the results with the AVPR2 and AQP2 reference sequence (GenBank accession no. NT025965 and AF147092).

Data analysis

Characteristics of study participants are presented as frequencies (percent) for categorical variables, means (SD) for normally distributed variables, and medians (25th to 75th percentile) for nonnormally distributed variables. Categorical variables were compared by Fisher's exact test and χ^2 test. Groups were compared by Kruskal-Wallis test among different groups followed by ANOVA and Holm's *post hoc* test to account for multiple testing. Nonnormally distributed variables were log normalized before entering ANOVA, and the respective r^2 values were used to express the correlation between continuous variables. To describe the diagnostic utility of a biomarker, standard diagnostic performance measures were calculated with their 95% confidence intervals (CIs), and receiver-operating characteristics were plotted. The area under the curve was calculated by the nonparametric trapezoidal rule, with its SE and 95% CI (22). Statistical analyses were performed using SPSS software (version 15.0.1, SPSS, Chicago, IL).

Results

Baseline characteristics

In total, 106 hyponatremic patients and 32 healthy control subjects were included in the study. The causes of hyponatremia were as follows: 4% primary polydipsia, 8% diuretic induced, 40% SIAD, 27% sodium depletion, and 21% sodium expansion. Baseline characteristics, including sex, age, and the most frequent disorders causing hyponatremia within categories are shown in Table 1. Details of the biochemical assessment are given in Table 2. Serum creatinine, urea, aldosterone, and renin values were significantly higher in the sodium depletion and sodium expansion group compared with the SIAD group, although there were no differences between the diuretic-induced group and SIAD group. Serum uric acid level was significantly lower and urinary sodium excretion significantly higher in the SIAD group compared with all other groups. FE-Na, FE-urea, and FE-K showed no significant differences between the groups.

Copeptin assay

As previously described for plasma AVP levels in healthy recumbent subjects (12), a close correlation between plasma copeptin and serum sodium ($r^2 = 0.62$, $P < 0.001$; Fig. 1A) and urine osmolality ($r^2 = 0.39$, $P = 0.001$; Fig. 1B) was observed in controls, reflecting AVP physiology (23).

Plasma copeptin levels and copeptin to U-Na ratio

The median copeptin values are presented in standard box and whisker plots for all tested groups (Fig. 2A). In controls, copeptin levels in men were significantly higher compared with women [7.2 (4.0–8.8) *vs.* 2.3 (1.2–3.9) pmol/liter; $P = 0.007$], whereas no sex differences were observed in patients. Compared with controls, copeptin levels were significantly higher in sodium-depleted, sodium-expanded, and SIAD patients (all $P < 0.001$), were similar in the diuretic-induced group, and were lower in patients with primary polydipsia ($P = 0.015$; Table 2). Using the combined information of plasma copeptin less than 3 pmol/liter and urine osmolality less than 200 mOsm/kg to diag-

TABLE 1. Baseline characteristics of hyponatremic patients (n = 106) and control subjects (n = 32)

Etiologic category	n (%)	Sex, male/female	Age, yr	Cause of hyponatremia
Primary polydipsia	4 (4)	0/5	61 (28)	Psychogenic polydipsia (100%)
Diuretic induced	9 (8)	1/8	76 (12)	Hydrochlorothiazide (100%)
SIAD	42 (40)	20/22	66 (14)	Neoplastic (48%) Acute bacterial infection (19%) Nausea and vomiting (18%) AVP analogues (4%) Positive pressure breathing (4%) Idiopathic (7%)
Sodium depletion	29 (27)	11/18	66 (17)	Gastrointestinal solute loss (31%) Malnutrition, loss of appetite (48%) Pancreatitis (21%)
Sodium expansion	22 (21)	16/6	67 (13)	Congestive heart failure (68%) Liver cirrhosis (23%) Angioedema (9%)
Controls	32 (10.7)	14/18	30 (7)	

Values are numbers or numbers (percent), as indicated. Age is given as mean (SD).

TABLE 2. Biochemical data before treatment in 106 hyponatremic patients and in 32 normal subjects

Diagnostic category	Primary polydipsia (n = 4)	Diuretic-induced (n = 9)	SIAD (n = 42)	Sodium depletion (n = 29)	Sodium expansion (n = 22)	Controls (n = 32)	*P* value
Serum and plasma							
Sodium, mmol/liter	123 (7)	121 (5)	125 (5)	124 (6)	125 (4)	139 (2)	0.462
Potassium, mmol/liter	3.8 (0.4)	3.8 (0.8)	4.2 (0.5)	4.1 (0.9)	4.3 (0.6)	4.3 (0.4)	0.561
Creatinine, mmol/liter	0.8 (0.2)	1.3 (1.2)	0.8 (0.3)	1.3 (0.6)[a]	1.2 (0.6)[a,b]	0.8 (1)	0.006
Urea, mg/dl	23 (6)	56 (51)	31 (16)	54 (29)[a,b]	81 (66)[a,b]	26 (7)	0.001
Uric acid, mg/dl	3.6 (1.2)[b]	6.6 (4.1)[a]	3.3 (1.5)[b]	7.5 (5.1)[a]	8.2 (3.8)[a]	4.8 (1.3)	<0.001
Aldosterone, ng/liter	99 (37–258)	65 (34–227)	53 (24–167)[b]	127 (49–360)[a]	253 (167–434)[a]	132 (63–220)	0.016
Renin, ng/liter	5 (1–9)	15 (5–257)	10 (5–23)	31(15–99)[a]	330 (54–730)[a]	9 (5–20)	<0.001
Copeptin, pmol/liter	2 (1−3)[a,b]	5 (3–23)	10 (4–21)[b]	16 (9–36)[a,b]	23 (10–50)[a,b]	4 (2–6)	0.002
[Copeptin/U–Na] ratio × 100	5 (2–9)	15 (3–34)[b]	12 (4–28)[b]	93 (34–187)[a,b]	49 (26–162)[a,b]	5 (2–7)[a]	<0.001
Urine							
Sodium, mmol/liter	43 (17)[§]	64 (32)[a]	94 (41)	29 (14)[a]	44 (27)[ab]	96 (22)	<0.001
Potassium, mmol/liter	11 (4)	27 (15)	42 (26)	45 (22)	45 (17)	48 (34)	0.003
Chloride, mmol/liter	33 (7)	68 (40)	95 (37)	53 (44)	53 (33)	136 (82)	0.001
Osmolality, mosm/kg	182 (50)[a]	283 (103)[a]	478 (170)	463 (218)	383 (127)	558 (304)	<0.001
Clearance ratio							
FE-Urea, %	50 (15)	39 (12)	50 (18)	31 (15)	32 (18)	50 (16)	<0.001
FE-Na, %	1.1 (0.3)	1.6 (0.5–4)	0.9 (0.5–1.8)	0.3 (0.1–0.6)	0.5 (0.2–1.2)	0.7 (0.2–1.3)	<0.001
FE-K, %	12 (6)	31 (15)[b]	16 (11)[b]	17 (12)[b]	21 (15)[b]	9 (4)	0.470

Data are mean (SD) or median (25th to 75th percentile), respectively. *P* value refers to Kruskal-Wallis testing across all subgroups except controls. FE, fractional excretion.

[a] $P < 0.05$ compared with SIAD (ANOVA with Holm's *post hoc* test).

[b] $P < 0.05$ compared with control (ANOVA with Holm's *post hoc* test).

nose or exclude primary polydipsia, these parameters correctly diagnosed primary polydipsia in 100% of the patients (Table 3), whereas urine osmolality of less than 200 mOsm/kg alone had a specificity of only 87%. In disorders with decreased effective arterial blood volume (sodium depleted and sodium expanded group), median copeptin values were significantly higher compared with the SIAD group ($P < 0.01$), whereas no differences were observed between the sodium depletion and sodium expansion groups.

To differentiate between volume-depleted disorders with secondary copeptin secretion (*i.e.* sodium depletion or sodium expansion) and normovolemic disorders with primary copeptin secretion (*i.e.* SIAD), we explored the copeptin to U-Na ratio: the copeptin to U-Na ratio in the SIAD group was significantly lower compared with the sodium depletion and sodium expansion groups ($P < 0.001$), whereas the overlap between the sodium depletion and SIAD groups as well as between the sodium expansion and SIAD groups was small (Fig. 2). Analyzing these three most challenging groups, the copeptin to U-Na ratio exhibited a good diagnostic utility identifying SIAD with an area under the receiver-operating characteristics curve of 0.88 (95% CI 0.81–0.95; $P < 0.001$). Choosing a cutoff value of less than 30 pmol/mmol, the copeptin to U-Na ratio had a sensitivity of 85%, specificity of 87%, positive predictive value of 85%, and

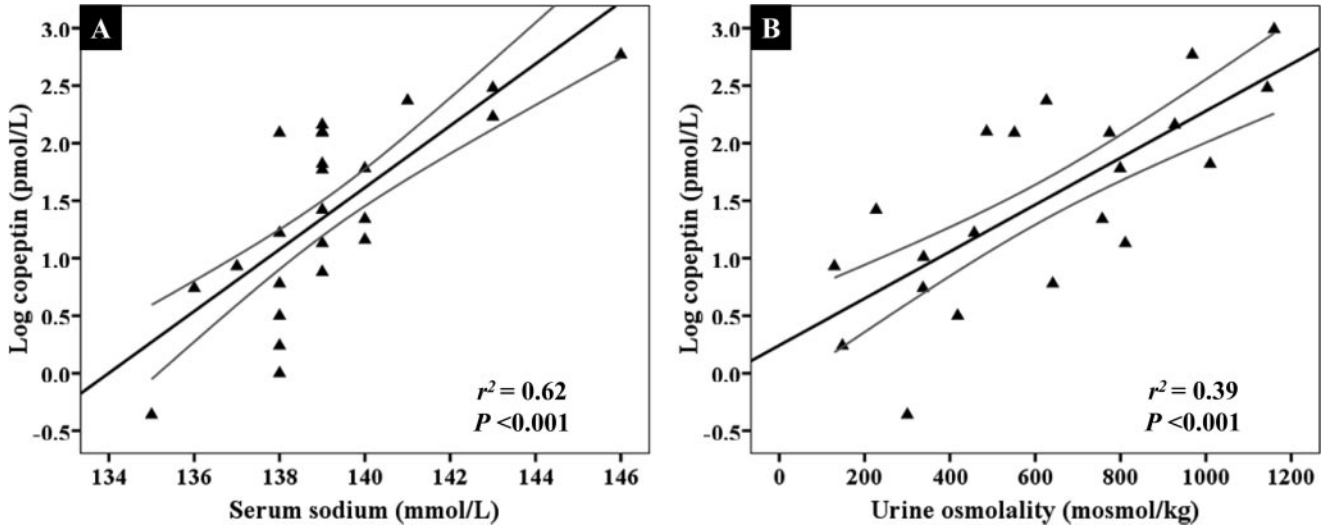

FIG. 1. Correlation between levels of log plasma copeptin (picomoles per liter) with serum sodium (A) and urine osmolality (B).

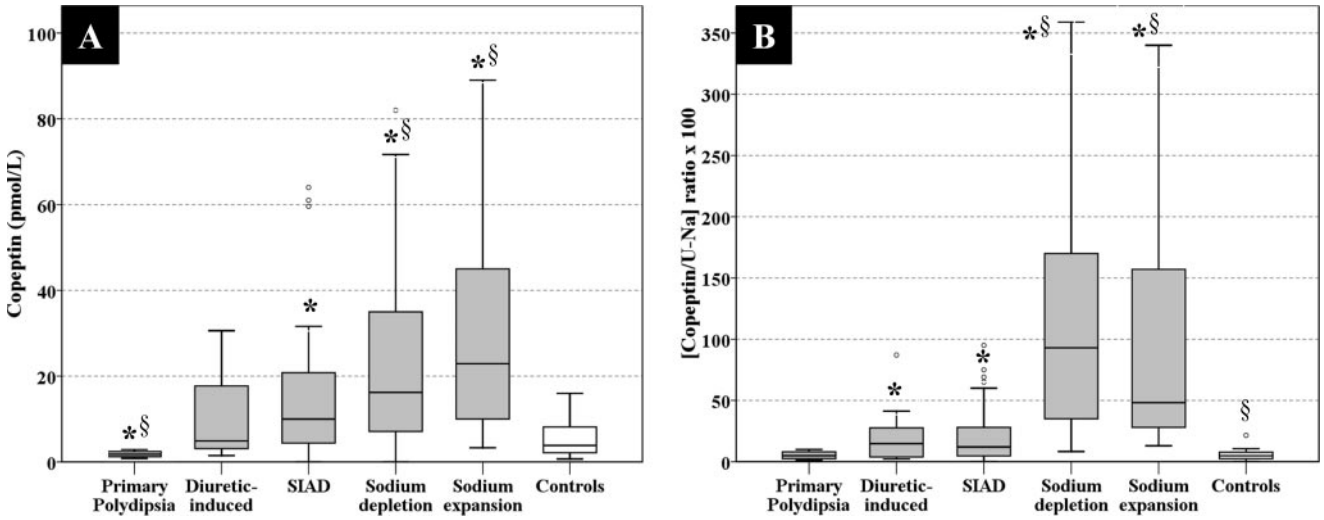

FIG. 2. Box and whisker plot for plasma copeptin levels (A) and the copeptin to U-Na ratio (B) in five diagnostic groups of hyponatremic patients (n = 106) and controls (n = 32). *, $P < 0.05$ compared with control (ANOVA with Holm's *post hoc* test); §, $P < 0.05$ compared with SIAD (ANOVA with Holm's *post hoc* test).

negative predictive value of 86% for SIAD (Table 3). Compared with the reference standard (U-Na, S-UA, FE-Na), the copeptin to U-Na ratio was clearly superior in specificity as well as in positive and negative predictive values ($P < 0.05$). There was no difference in the copeptin to U-Na ratio between the SIAD and diuretic-induced groups ($P = 0.98$).

DNA sequencing of three patients with hypovasopressinergic antidiuresis

Five of 42 patients (12%) exhibited all criteria for SIAD, whereas plasma copeptin levels were undetectable or close to the detection limit (Table 4). Referring to Decaux *et al.* (24) and Feldman *et al.* (25), who recently reported a gain-of-function mutation in the vasopressin-2 receptor (V2R), the entire coding regions of the V2R and aquaporine-2 (AQP2) gene were amplified in the three surviving patients. No mutations were found in the DNA sequences of V2R and AQP2 in all three patients.

Discussion

The current study is the first to investigate the diagnostic utility of plasma copeptin measurements in the diagnostic approach to hyponatremia in a typical clinical setting. Our findings indicate that plasma copeptin is a suitable surrogate of AVP secretion in hyponatremic disorders with varying hormone levels, depending on underlying pathomechanisms: in all patients with AVP-dependent hyponatremia plasma copeptin concentrations were significantly higher compared with controls (12, 23). Copeptin levels were suppressed in primary polydipsia and were stimulated significantly more in disorders with decreased effective arterial blood volume compared with SIAD (26, 27).

In patients with primary polydipsia, a suppressed copeptin value (<3 pmol/liter) in the context of an appropriate urine dilution (urine osmolality < 200 mOsm/kg) corrected the discriminatory capacity for identifying these patients to 100%.

However, the actual diagnostic challenge in clinical practice is to discern patients with SIAD and patients with sodium depletion. Although median copeptin values were significantly higher in sodium-depleted patients compared with SIAD, copeptin measurement could not reliably differentiate between these disorders because of a large overlap in copeptin values (Fig. 2). Thus, copeptin is of limited diagnostic value in patients with AVP-dependent hyponatremia. In contrast, the copeptin to U-Na ratio proved diagnostically most useful. The combined information of salt retention and copeptin release in this index is

TABLE 3. Diagnostic utility of plasma copeptin in the clinical differential diagnosis of primary polydipsia and SIAD

	Test parameter	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Primary polydipsia[a]	Plasma copeptin < 3 pmol/liter and urine osmolality < 200 mOsm/kg	100	100	100	100
SIAD (n = 42)[b]	Copeptin/U to Na × 100 < 30 pmol/mol	85	87	85	86
	U-Na > 30 mmol/liter	82	53	58	78
	Serum urate < 4 mg/dl	73	82	76	79
	FE-Na > 0.5%	71	60	57	73

FE, Fractional excretion.

[a] The diagnostic sample considers all hyponatremic patients (n = 106) to diagnose/exclude primary polydipsia (n = 4).

[b] The diagnostic sample considers only patients from SIAD, sodium depletion, and sodium expansion groups (n = 93) to diagnose/exclude SIAD (n = 42).

TABLE 4. Characteristics of five patients with SIAD and plasma copeptin concentration of 1.9 pmol/liter or less

Patient number	Plasma copeptin, pmol/liter	Serum osmolality, mOsmol/kg	Serum sodium, mmol/liter	Urine sodium, mOsmol/kg	Urine osmolality, mmol/liter
1	<0.5	250	122	45	320
2[a]	1.0	270	127	146	573
3	1.9	250	124	150	528
4	1.9	257	126	70	262
5[a]	1.5	258	126	104	561

[a] These patients died before blood for genetic analysis was collected.

an accurate method to differentiate primary from secondary copeptin release. Compared with the established reference standard (U-Na, serum urate level, and fractional sodium excretion), a copeptin to U-Na ratio of less than 30 pmol/mmol was superior in identifying SIAD (Table 3), also compared with other ratios like S-Urate to U-Na ratio less than 10.

Interestingly, comparing the SIAD and diuretic-induced group, we found no differences in copeptin values, copeptin to U to Na ratio, or any other volume-related parameter including plasma aldosterone or renin concentration. Although diuretic-induced hyponatremia is commonly considered to be associated with volume depletion (3, 5), several studies described patients with thiazide-induced hyponatremia without concomitant clinical features of dehydration (28–30). Our data are consistent with these findings, even though raised serum uric acid levels and normal FE-urate in the diuretic group separated patients with diuretic-induced hyponatremia from those with SIAD (29).

Taken together, these analyses of plasma copeptin in hyponatremia will improve less essentially our diagnostic precision than contribute to our pathophysiological understanding of the different causes of hyponatremia. In addition to its unique potential to distinguish antidiuretic activity due to AVP from effects secondary to other hormonal proteins or intrarenal factors, copeptin may be of particular interest in clarifying the different osmoregulatory defects in patients with SIAD. Four different SIAD types have been described (31, 32) based on changes in AVP levels occurring with increments of raised plasma osmolality (33). Although the pathogenesis of the different types of SIAD is still not fully understood, treatment response is suggested to vary substantially, depending on the underlying antidiuretic defect (31). Of particular interest in this context is the hypovasopressinemic type or SIAD type D (33). Although no defect in the osmoregulation of plasma AVP could be demonstrated so far, these patients fail to dilute their urine or increase their urine flow after a water load (31). This suggests that inappropriate antidiuresis may be linked to mechanisms other than AVP hypersecretion.

A gain-of-function mutation in the AVP receptor type 2 has been identified in this context as a new mechanism that may increase free water reabsorption in these patients (24, 25). Interestingly, in all of our SIAD patients compatible with type D (Table 4), no mutations were detected in the DNA sequence of both AVPR2 and AQP2, suggesting the presence of further disorders of tubular water reabsorption, like an intrinsic renal defect in urinary dilution or the production of antidiuretic peptides not related to AVP. In addition to its enigmatic pathogenesis, SIAD type D also presents a therapeutic challenge because treatment with a competitive V2R antagonist will be ineffective in these patients. A causal relation between SIAD type D and a lack of response to vaptan administration (34) has been suggested (31) but has not yet been studied, probably due to the difficulties related to AVP measurement. If the types of osmoregulatory defects in SIAD as described by Zerbe *et al.* (33) will be reproducible using plasma copeptin measurements, copeptin may facilitate the identification of the type of osmoregulatory defect in SIAD and predict the treatment response in individual patients. In addition, the measurement of plasma copeptin may become a robust and rapidly available parameter to screen for activating AVP2R mutations as a cause of hyponatremia.

In conclusion, we demonstrated that copeptin concentrations also mirror AVP release in hyponatremic disorders as has been demonstrated for other clinical settings. Plasma copeptin measurement in combination with the assessment of urine osmolality is a simple test to confirm the clinical diagnosis of primary polydipsia with high accuracy. To differentiate between SIAD and disorders with sodium depletion, the copeptin to U-Na ratio appears to be a useful index and superior to the established reference standard. In addition, copeptin may become a useful diagnostic tool in patients with SIAD to predict the response to V2R antagonists and may help to identify hyponatremic patients with activating AVP2R mutations.

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Address all correspondence and requests for reprints to: Professor Dr. Bruno Allolio, M.D., Endocrinology and Diabetes Unit, Department of Medicine I, University of Würzburg, Josef-Schneider-Strasse 2, D-97080 Würzburg, Germany. E-mail: allolio_b@medizin.uni-wuerzburg.de.

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