ORIGINAL ARTICLE

A Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus

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ABSTRACT

BACKGROUND

The indirect water-deprivation test is the current reference standard for the diagnosis of diabetes insipidus. However, it is technically cumbersome to administer, and the results are often inaccurate. The current study compared the indirect water-deprivation test with direct detection of plasma copeptin, a precursor-derived surrogate of arginine vasopressin.

METHODS

From 2013 to 2017, we recruited 156 patients with hypotonic polyuria at 11 medical centers to undergo both water-deprivation and hypertonic saline infusion tests. In the latter test, plasma copeptin was measured when the plasma sodium level had increased to at least 150 mmol per liter after infusion of hypertonic saline. The primary outcome was the overall diagnostic accuracy of each test as compared with the final reference diagnosis, which was determined on the basis of medical history, test results, and treatment response, with copeptin levels masked.

RESULTS

A total of 144 patients underwent both tests. The final diagnosis was primary polydipsia in 82 patients (57%), central diabetes insipidus in 59 (41%), and nephrogenic diabetes insipidus in 3 (2%). Overall, among the 141 patients included in the analysis, the indirect water-deprivation test determined the correct diagnosis in 108 patients (diagnostic accuracy, 76.6%; 95% confidence interval [CI], 68.9 to 83.2), and the hypertonic saline infusion test (with a copeptin cutoff level of >4.9 pmol per liter) determined the correct diagnosis in 136 patients (96.5%; 95% CI, 92.1 to 98.6; P<0.001). The indirect water-deprivation test correctly distinguished primary polydipsia from partial central diabetes insipidus in 77 of 105 patients (73.3%; 95% CI, 63.9 to 81.2), and the hypertonic saline infusion test distinguished between the two conditions in 99 of 104 patients (95.2%; 95% CI, 89.4 to 98.1; adjusted P<0.001). One serious adverse event (desmopressin-induced hyponatremia that resulted in hospitalization) occurred during the water-deprivation test.

CONCLUSIONS

The direct measurement of hypertonic saline–stimulated plasma copeptin had greater diagnostic accuracy than the water-deprivation test in patients with hypotonic polyuria. (Funded by the Swiss National Foundation and others; ClinicalTrials.gov number, NCT01940614.)

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The determination of a specific diagnosis in patients with polyuria and low plasma osmolality (i.e., hypotonic polyuria) is a frequent problem in clinical practice. In the absence of osmotic diuresis, polyuria can result from one of three fundamentally different conditions[1]: insufficient production and secretion of the antidiuretic hormone arginine vasopressin (central diabetes insipidus), diminished renal sensitivity to the antidiuretic activity of arginine vasopressin (nephrogenic diabetes insipidus), or primary excessive fluid intake (primary polydipsia).

It is important to differentiate these entities because treatments differ substantially, and incorrect strategies may lead to severe complications.[2,3] The indirect water-deprivation test measures the maximal urine concentration during prolonged withholding of oral liquids and the renal response to administered desmopressin.[4] It is conceptually simple, but difficulties in interpretation are common, mainly because any water diuresis may compromise the renal medullary concentration gradient[1,5,6] and promote a downregulation of kidney aquaporin-2 water channels, which could potentially affect the diagnostic value of these urinary measures.[5] Previous attempts to improve the diagnosis of polyuric disorders with direct measurement of circulating arginine vasopressin[7-10] failed to gain traction in clinical practice, largely because of the technical difficulties of measuring arginine vasopressin.[11-14]

Copeptin, the C-terminal segment of the arginine vasopressin prohormone, is an arginine vasopressin surrogate with high ex vivo stability that is easy to measure.[12,15,16] In previous studies, we reported outcome data that suggested that measurement of osmotically stimulated copeptin might be useful in differentiating the various causes of hypotonic polyuria.[5,17-19] The current study assessed the diagnostic performance of a test measuring copeptin that was osmotically stimulated by water deprivation or by hypertonic saline infusion as compared with the indirect water-deprivation test.

Methods

Study Design and Patients

This international, multicenter, prospective study was conducted at 11 tertiary medical centers in Switzerland, Germany, and Brazil from July 2013 to June 2017; the 3-month follow-up visits were completed by September 2017. We recruited 156 patients 16 years of age or older with hypotonic polyuria (a urine output of >50 ml per kilogram of body weight during a 24-hour period, with a urine osmolality <800 mOsm per kilogram) or with a confirmed diagnosis of central diabetes insipidus. Three patients were excluded from the analyses because they were found to have nephrogenic diabetes insipidus, and 12 patients were excluded for other reasons (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The local ethics committees at all centers approved the study protocol (available at NEJM.org). Written informed consent was obtained from all patients or from a legal guardian, when applicable. Laboratory measurement of copeptin was funded by Thermo Fisher Scientific, which had no other role in the study; there was no other commercial support for the study. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Procedures at Baseline

The water-deprivation and hypertonic saline infusion tests were performed on separate days. After a detailed medical history was obtained, a standardized clinical and biochemical evaluation was performed. Magnetic resonance imaging (MRI) of the head was performed at the discretion of the attending physician, although it was recommended in all patients if imaging had not been performed within 3 months before study enrollment. Diuretic or antidiuretic medications were discontinued for at least 24 hours before each test, and smoking and alcohol were prohibited for at least 12 hours before each test.

Test Protocols

Indirect Water-Deprivation Test

As is standard for the water-deprivation test,[4] a 17-hour fluid restriction started at midnight, or at 6 a.m. in patients with known or suspected complete diabetes insipidus. Every 2 hours, vital signs and body weight were monitored and urine was collected for measurement of volume and osmolality. Blood samples were obtained at 8 a.m. and immediately before the administration of desmopressin (1 hour before the end of the test).

For safety reasons, the water-deprivation test was stopped early in patients who met one of the following criteria: a decrease in body weight of more than 3%, symptoms of orthostatic hypotension with an increase in heart rate or a decrease in mean arterial blood pressure of more than 15%, or an increase in plasma sodium level of 150 mmol or more per liter. At 4 p.m., or when the test was stopped, each patient received 2 μg of desmopressin intravenously, and a final urine specimen for osmolality measurement was obtained at least 60 minutes thereafter.

Hypertonic Saline Infusion Test

Patients underwent the hypertonic saline infusion test between 8 a.m. and 11 a.m., as described previously.[16] An initial 250-ml bolus infusion of 3% saline was administered, and the infusion was continued at a rate of 0.15 ml per kilogram per minute. Blood samples for the measurement of plasma osmolality and sodium, urea, and glucose levels were obtained every 30 minutes, and sodium levels were monitored by venous blood gas analysis until the target level of at least 150 mmol per liter was reached. Thereafter, a final blood sample for plasma copeptin measurement was obtained, and patients were given water orally (30 ml of water per kilogram) within 30 minutes, followed by a 500-ml infusion of 5% glucose within 40 to 60 minutes after the patients received water. For safety reasons, the plasma sodium level was measured again 1 hour after the start of the glucose infusion to ensure that the level was within the normal range before the patient was discharged.

ADVERSE EVENTS AND SYMPTOM BURDEN

Adverse events during both tests were strictly documented, and clinical symptoms were rated by patients according to a visual-analogue scale that ranged from 0 to 10, with 0 indicating no symptoms and 10 indicating the most severe symptoms imaginable. Additional details are provided in the Supplementary Appendix.

TEST INTERPRETATION AND PRELIMINARY DIAGNOSIS

After the patients had completed both tests, they were discharged from the hospital with a preliminary diagnosis and treatment recommendation that were based on best current clinical practice. A follow-up visit was scheduled for 3 months later to assess response to treatment and clinical outcome and to reevaluate the accuracy of the preliminary diagnosis.

DIAGNOSTIC CRITERIA

Indirect Water-Deprivation Test

In accordance with the original description of the indirect water-deprivation test[4] and the subsequent modification,[5,8,20] complete central diabetes insipidus was diagnosed in patients who had a maximum urine osmolality of less than 300 mOsm per kilogram and an increase in urine osmolality of more than 50% after administration of desmopressin. Partial central diabetes insipidus was diagnosed in patients who had a maximum urine osmolality of 300 to 800 mOsm per kilogram and an increase in urine osmolality of 9 to 50% after administration of desmopressin. Primary polydipsia was diagnosed in patients who had a maximum urine osmolality of 300 to 800 mOsm per kilogram and an increase in urine osmolality of less than 9% after administration of desmopressin.

Plasma Copeptin Stimulated by Water Deprivation

Previous data suggested that the diagnostic accuracy of the indirect water-deprivation test could be improved by the additional measurement of baseline (at 8 a.m.) as well as stimulated (before administration of desmopressin) plasma copeptin levels.[5] According to those results, prespecified cutoff levels were used: a ratio of stimulated copeptin (the change in copeptin level over 8 hours during water deprivation, in picomoles per liter) to plasma sodium (measured at the end of the test in millimoles per liter) of 0.02 pmol or more per liter indicated primary polydipsia, and a basal plasma copeptin level of less than 2.6 pmol per liter indicated complete central diabetes insipidus. A ratio of less than 0.02 pmol per liter indicated partial central diabetes insipidus.

Plasma Copeptin Stimulated by Hypertonic Saline Infusion

The diagnostic criteria for hypertonic saline–stimulated copeptin in distinguishing primary polydipsia from central diabetes insipidus were suggested previously by our group[19] and were used in this study. A plasma copeptin cutoff level of 4.9 pmol or less per liter indicated complete or

partial central diabetes insipidus, and a level greater than 4.9 pmol per liter indicated primary polydipsia.

FINAL REFERENCE DIAGNOSIS

In the absence of a diagnostic standard, the final reference diagnosis was determined after the study was completed by two independent board-certified experts in endocrinology, who were unaware of the copeptin levels, after careful consideration of each patient's medical history and clinical symptoms, the results of the water-deprivation test, the available laboratory and imaging data, and the therapeutic response at the 3-month follow-up. In the event of discordant diagnoses (which occurred in 4 of 144 patients), a third expert was consulted, and results were discussed until a consensus was reached.

LABORATORY MEASUREMENTS

Blood samples were obtained and processed for measurement of plasma copeptin and for routine laboratory measurements (urine and plasma osmolality, hematocrit, and plasma sodium, potassium, creatinine, urea, calcium, albumin, glucose, and hemoglobin levels). Plasma copeptin was measured centrally in one batch with the use of a commercial automated immunofluorescence assay (B.R.A.H.M.S KRYPTOR Copeptin proAVP, Thermo Scientific Biomarkers). Details are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary end point was the overall diagnostic accuracy — the percentage of correctly diagnosed patients — in the differentiation of central diabetes insipidus from primary polydipsia. Only patients with a final diagnosis were included in the analysis; however, the three patients with nephrogenic diabetes insipidus were only descriptively assessed. Details concerning the full-analysis population and the per-protocol population, as well as additional statistical details, are provided in the Supplementary Appendix.

The primary objectives were first to determine whether the measurement of copeptin during hypertonic saline infusion and during water deprivation was superior to the indirect water-deprivation test, and then to determine whether copeptin measurement during hypertonic saline infusion was noninferior to copeptin measurement during water deprivation; the second objective would be tested only if superiority could be shown for the first objective. The primary hypothesis thus consisted of two components, with a two-step statistical testing procedure. Sample size was estimated for the noninferiority test: assuming a diagnostic accuracy of 90% for water-deprivation–stimulated copeptin[5] and a noninferiority margin of 10%, a total of 115 patients who could be evaluated would provide 90% power to establish the noninferiority of hypertonic saline–stimulated copeptin measurement to water-deprivation–stimulated copeptin measurement. To assess whether the diagnostic accuracy varied depending on the severity of central diabetes insipidus, a prespecified subgroup analysis was performed to assess the diagnostic accuracy of hypertonic saline–stimulated copeptin and water-deprivation–stimulated copeptin as compared with the indirect water-deprivation test in specifically distinguishing primary polydipsia from partial central diabetes insipidus.

RESULTS

BASELINE CHARACTERISTICS

Of the 141 patients (66% female) included in the analyses, 82 (58%) received a final diagnosis of primary polydipsia after all 3-month follow-ups were completed, and 59 (42%) received a diagnosis of central diabetes insipidus (Fig. S1 in the Supplementary Appendix). Among the 59 patients who received a diagnosis of central diabetes insipidus, complete central diabetes insipidus was diagnosed in 36 patients (61%), and partial central diabetes insipidus in 23 (39%).

There were significant differences between the groups in some baseline characteristics (Table 1). Results of MRI of the head were available for 97 patients. The hyperintense signal in the posterior region on T_1-weighted images, which is considered to be a physiological signal that indicates the pituitary arginine vasopressin content,[21,22] was absent in 70% of the patients with central diabetes insipidus, but it was also absent in 39% of the patients with primary polydipsia (Table 1).

PRIMARY OUTCOME

The overall diagnostic accuracy of the hypertonic saline infusion test was significantly higher than that of the indirect water-deprivation test

Table 1. Baseline Characteristics of the Patients with Hypotonic Polyuria, According to Final Reference Diagnosis.*

Characteristic	Central Diabetes Insipidus			Primary Polydipsia (N = 82)
	Complete Diabetes Insipidus (N = 36)	Partial Diabetes Insipidus (N = 23)	All Central Diabetes Insipidus (N = 59)	
Median age (IQR) — yr	48 (39–53)	43 (30–48)	45 (33–53)	32 (24–44)
Female sex — no. (%)	23 (64)	15 (65)	38 (64)	55 (67)
Median body-mass index (IQR)†	29 (25–31)	26 (23–32)	28 (24–31)	24 (21–26)
Clinical symptoms				
Polydipsia — median liters consumed/day (IQR)	6.0 (5.0–8.6)	5.5 (4.0–6.5)	6.0 (4.8–8.0)	5.0 (4.5–6.9)
Polyuria — median liters of urine/day (IQR)	6.0 (4.9–8.0)	4.0 (3.5–6.0)	5.0 (4.0–7.8)	5.0 (4.0–6.0)
Nocturia — no. (%)	35 (97)	21 (91)	56 (95)	56 (68)
Median no. of events/night (IQR)	3 (2–4)	3 (2–5)	3 (2–4)	1 (0–3)
Drinking at night — no. (%)	33 (92)	21 (91)	54 (92)	51 (62)
Median liters consumed/night (IQR)	1.5 (1.0–2.0)	1.0 (0.5–2.0)	1.3 (0.9–2.0)	0.2 (0–0.6)
Preference for cold drinks — no. (%)	26 (72)	18 (78)	44 (75)	49 (60)
Preference for water — no./total no. (%)	32/34 (94)	19/22 (86)	51/56 (91)	73/80 (91)
Sudden onset of symptoms — no. (%)	22 (61)	15 (65)	37 (63)	18 (22)
Persistent symptoms — no. (%)	34 (94)	22 (96)	56 (95)	64 (78)
Polyuria preceding manifestation of polydipsia — no. (%)	3 (8)	2 (9)	5 (9)	3 (4)
Onset of symptoms coinciding with stressful emotional or physical event — no./total no. (%)	2/36 (6)	7/23 (30)	9/59 (15)	15/81 (19)
Medical history — no. (%)				
Brain tumor	17 (47)	12 (52)	29 (49)	5 (6)
Transsphenoidal surgery	20 (56)	10 (44)	30 (51)	2 (2)
Anterior pituitary insufficiency	25 (69)	12 (52)	37 (63)	2 (2)
Psychiatric disorder	10 (28)	0	10 (17)	22 (27)

MRI characteristics — no./total no. (%)				
MRI performed during the study period	33/36 (92)	22/23 (96)	55/59 (93)	42/82 (51)
Hyperintense signal in posterior pituitary absent	21/26 (81)	12/21 (57)	33/47 (70)	14/36 (39)
Pituitary stalk enlarged	6/30 (20)	3/22 (14)	9/52 (17)	1/39 (3)
Hyperintense signal in posterior pituitary absent and pituitary stalk enlarged	3/26 (12)	2/21 (10)	5/47 (11)	1/36 (3)
Laboratory data				
Median plasma sodium — mmol/liter (IQR)	142 (140–143)	143 (142–144)	142 (141–144)	141 (139–142)
Median plasma osmolality — mOsm/kg (IQR)	291 (286–296)	294 (291–301)	292 (288–298)	287 (283–291)
Median urine osmolality — mOsm/kg (IQR)	176 (95–231)	421 (252–460)	228 (116–380)	408 (237–576)

* There were significant between-group differences in age, body-mass index, nocturia, drinking at night, sudden onset of symptoms, persistency of symptoms, history of brain tumor, history of transsphenoidal surgery, anterior pituitary insufficiency, absent hyperintense signal in posterior pituitary, enlargement of pituitary stalk, plasma sodium, plasma osmolality, and urine osmolality. IQR denotes interquartile range, and MRI magnetic resonance imaging.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

(96.5% [95% confidence interval {CI}, 92.1 to 98.6] vs. 76.6% [95% CI, 68.9 to 83.2]; P<0.001) (Table 2). The diagnostic accuracy of the hypertonic saline infusion test was also clearly superior to that of the indirect water-deprivation test when only patients with partial central diabetes insipidus were compared with patients with primary polydipsia (95.2% [95% CI, 89.4 to 98.1] vs. 73.3% [95% CI, 63.9 to 81.2]; adjusted P<0.001) (Table 2). Additional details on the test results are provided in Table S1 in the Supplementary Appendix.

The copeptin level measured after hypertonic saline infusion more accurately distinguished primary polydipsia from central diabetes insipidus than the water-deprivation test with or without copeptin measurement (Fig. 1). Additional details on the course of copeptin levels during hypertonic saline infusion are provided in Fig. S2 in the Supplementary Appendix. The prespecified hypertonic saline–stimulated copeptin cutoff level of more than 4.9 pmol per liter[19] had a 93.2% sensitivity (95% CI, 83.5 to 98.1) and 100% specificity (95% CI, 95.5 to 100.0) to discriminate between primary polydipsia and central diabetes insipidus (Table 2), with a receiver-operating-characteristic area under the curve for this discrimination of 0.97 (95% CI, 0.93 to 1.00). The most accurate copeptin cutoff level was 6.5 pmol per liter (derived post hoc), which had a diagnostic accuracy of 97.9% (95% CI, 93.9 to 99.6), sensitivity of 94.9% (95% CI, 85.9 to 98.9), and specificity of 100% (95% CI, 95.5 to 100.0) (Fig. 2 and Table 2).

The overall diagnostic accuracy of water-deprivation–stimulated copeptin (with use of the prespecified ratio of stimulated copeptin to plasma sodium described above) in distinguishing primary polydipsia from central diabetes insipidus[5] was significantly lower than that of the indirect water-deprivation test (44.0% [95% CI, 35.7 to 52.5] vs. 76.6% [95% CI, 68.9 to 83.2]) (Table 2). When the prespecified morning copeptin cutoff level of less than 2.6 pmol per liter after overnight water deprivation was used to identify patients with complete central diabetes insipidus,[5] the diagnostic accuracy was 78.4% (95% CI, 70.6 to 84.9). Plasma copeptin values after overnight water deprivation and the associated receiver-operating-characteristic area under the curve are provided in Figure S3 in the Supplementary Appendix.

Table 2. Diagnostic Performance of the Indirect Water-Deprivation Test, the Water-Deprivation–Stimulated Copeptin Test, and the Hypertonic Saline–Stimulated Copeptin Test.*

Comparison and Test	Diagnostic Accuracy		Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value	
	% (95% CI)	no./total no.	% (95% CI)	no./total no.	% (95% CI)	no./total no.	% (95% CI)	no./total no.	% (95% CI)	no./total no.
Primary polydipsia vs. central diabetes insipidus										
Indirect water-deprivation test	76.6 (68.9–83.2)	108/141	86.4 (75.0–94.0)	51/59	69.5 (58.4–79.2)	57/82	67.1 (55.4–77.5)	57/76	87.7 (77.2–94.5)	57/65
Water-deprivation–stimulated copeptin†	44.0 (35.7–52.5)	62/141	98.3 (90.9–100.0)	58/59	5.0 (1.4–12.3)	4/80	43.3 (34.8–52.1)	58/134	80.0 (28.4–99.5)	4/5
Hypertonic saline–stimulated copeptin with >4.9 pmol/liter cutoff‡	96.5 (92.1–98.6)	136/141	93.2 (83.5–98.1)	55/59	100.0 (95.5–100.0)	81/81	100.0 (93.5–100.0)	55/55	95.3 (88.4–98.7)	81/85
Hypertonic saline–stimulated copeptin with >6.5 pmol/liter cutoff§	97.9 (93.9–99.6)	137/140	94.9 (85.9–98.9)	56/59	100.0 (95.5–100.0)	81/81	100.0 (93.6–100.0)	56/56	96.4 (89.9–99.3)	81/84
Primary polydipsia vs. partial central diabetes insipidus										
Indirect water-deprivation test	73.3 (63.9–81.2)	77/105	87.0 (66.4–97.2)	20/23	69.5 (58.4–79.2)	57/82	44.4 (29.6–60.0)	20/45	95.0 (86.1–99.0)	57/60
Water-deprivation–stimulated copeptin†	25.2 (17.2–34.8)	26/103	95.7 (78.1–99.9)	22/23	5.0 (1.4–12.3)	4/80	22.4 (14.6–32.0)	22/98	80.0 (28.4–99.5)	4/5
Hypertonic saline–stimulated copeptin with >4.9 pmol/liter cutoff‡	95.2 (89.4–98.1)	99/104	82.6 (61.2–95.0)	19/23	100.0 (95.5–100.0)	81/81	100.0 (82.4–100.0)	19/19	95.3 (88.4–98.7)	81/85
Hypertonic saline–stimulated copeptin with >6.5 pmol/liter cutoff§	97.1 (91.8–99.4)	101/104	87.0 (66.4–97.2)	20/23	100.0 (95.5–100.0)	81/81	100.0 (83.2–100.0)	20/20	96.4 (89.9–99.3)	81/84

* A total of 141 patients underwent both the water-deprivation test and the hypertonic saline–stimulated copeptin test. For the assessment of the primary outcome of diagnostic accuracy, missing copeptin measurements were imputed as false results (two for the water-deprivation test and one for the hypertonic saline infusion test). Sensitivity, specificity, positive predictive value, and negative predictive value were calculated according to the number of patients with complete data (141 for the indirect water-deprivation test, 139 for water-deprivation–stimulated copeptin, and 140 for hypertonic saline–stimulated copeptin).

† A ratio of stimulated copeptin (the change in copeptin level over 8 hours during water deprivation in picomoles per liter) to plasma sodium (measured at the end of the test in millimoles per liter) of 0.02 pmol or more per liter indicated primary polydipsia, and a basal plasma copeptin level less than 2.6 pmol per liter indicated central diabetes insipidus. A ratio of less than 0.02 pmol per liter indicated partial central diabetes insipidus.

‡ A prespecified copeptin level of more than 4.9 pmol per liter indicated primary polydipsia, and a level of 4.9 pmol or less per liter indicated complete or partial central diabetes insipidus.

§ In a secondary analysis, a copeptin level of more than 6.5 pmol per liter indicated primary polydipsia, and a level of 6.5 pmol or less per liter indicated complete or partial central diabetes insipidus.

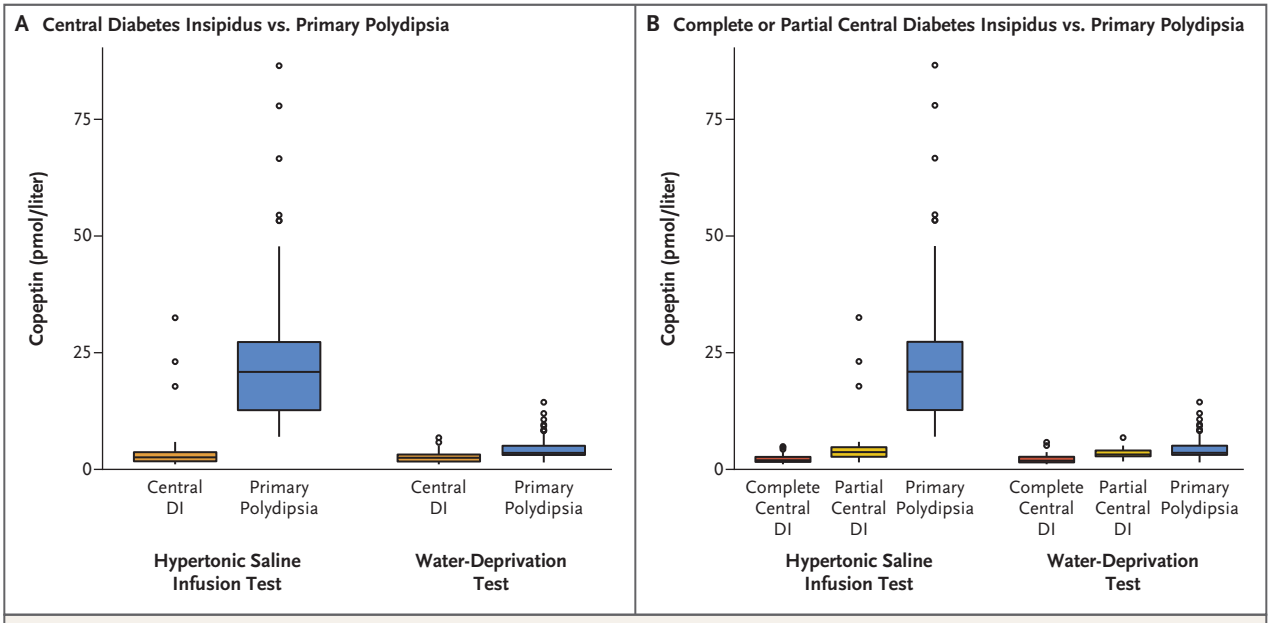

Figure 1. Stimulated Copeptin Levels in Response to the Hypertonic Saline Infusion and Water-Deprivation Tests in Patients with Hypotonic Polyuria.

Shown are stimulated copeptin levels in response to the hypertonic saline infusion test and water-deprivation test in patients with hypotonic polyuria that was caused by central diabetes insipidus as compared with primary polydipsia (Panel A) and in patients with hypotonic polyuria that was caused by complete central diabetes insipidus or partial central diabetes insipidus as compared with primary polydipsia (Panel B). The horizontal line in each box represents the median, the lower and upper boundaries of the boxes the interquartile range, the ends of the whisker lines the minimum and maximum values within 1.5 times the interquartile range, and the dots outliers. DI denotes diabetes insipidus.

SECONDARY OUTCOMES AND BURDEN OF TESTS

Patients rated the overall burden of the water-deprivation test higher than that of the hypertonic saline infusion test (median score on the visual-analogue scale, 6 [interquartile range, 4 to 7] vs. 5 [interquartile range, 3 to 6]) and the overall tolerability (i.e., convenience of the test and patients' comfort level during the test) lower (38% of patients preferred the water-deprivation test, whereas 62% preferred the hypertonic saline infusion test) (Table 3). The plasma sodium level increased to more than 155 mmol per liter in 12 patients during hypertonic saline infusion (in 6 patients with a final diagnosis of primary polydipsia, 5 with complete central diabetes insipidus, and 1 with partial central diabetes insipidus), as compared with 2 patients during water deprivation (both patients had complete central diabetes insipidus). All 12 patients were female and had baseline plasma sodium levels of 140 to 144 mmol per liter. Additional information on the course of plasma sodium level during hypertonic saline infusion is provided in Figure S4 in the Supplementary Appendix.

Nine adverse events occurred during hypertonic saline infusion, and seven during water deprivation. One serious adverse event was reported: desmopressin-induced hyponatremia after the water-deprivation test, which resulted in hospitalization of the patient (Table 3).

DISCUSSION

This prospective, multicenter study showed that measurement of hypertonic saline–stimulated copeptin was superior to the indirect water-deprivation test in distinguishing polyuria due to primary polydipsia from polyuria due to central diabetes insipidus. However, the postulated superiority of water-deprivation–stimulated copeptin to the indirect water-deprivation test could not be confirmed in this study. The diagnostic accuracy of the indirect water-deprivation test of approximately 70% in our study, which is consis-

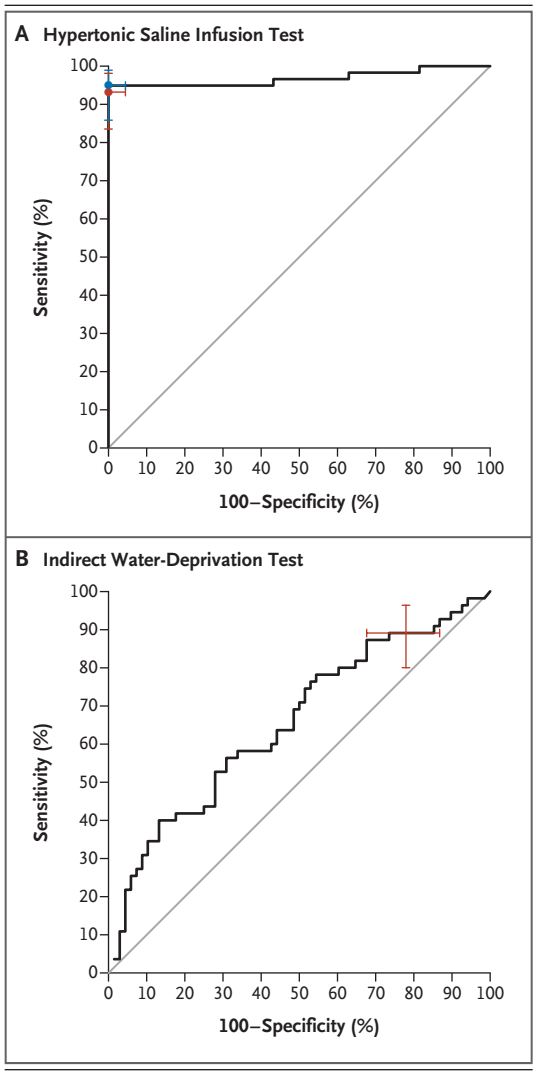

Figure 2. Receiver-Operating-Characteristic (ROC) Curves for the Hypertonic Saline Infusion Test and the Indirect Water-Deprivation Test.

Shown are the ROC curves for the discriminative accuracy of the hypertonic saline infusion test and the indirect water-deprivation test. Panel A shows the discriminative accuracy of hypertonic saline–stimulated copeptin levels in differentiating primary polydipsia from central diabetes insipidus (area under the curve [AUC], 0.97; 95% CI, 0.93 to 1.00). The copeptin cutoff level of 4.9 pmol per liter (prespecified) is indicated in red, and the cutoff of 6.5 pmol per liter (derived post hoc) is indicated in blue. I bars in Panel A indicate 95% confidence intervals. Panel B shows the discriminative accuracy of the indirect water-deprivation test (which measures the change in urine osmolality before and after administration of desmopressin) in differentiating primary polydipsia from central diabetes insipidus (AUC, 0.65; 95% CI, 0.56 to 0.75). I bars in Panel B indicate the 95% confidence intervals for the sensitivity and specificity of the indirect water-deprivation test at a 9% cutoff for the increase in urine osmolality after administration of desmopressin. The gray diagonal lines represent the results that would be expected by chance alone.

tent with previous findings in smaller studies,[5,8] resulted in approximately 30% of patients with primary polydipsia incorrectly receiving a diagnosis of central diabetes insipidus. All the patients in the current study whose diagnosis was misclassified according to the indirect water-deprivation test received the correct diagnosis according to the results of the hypertonic saline infusion test with the prespecified copeptin cutoff of 4.9 pmol per liter.

As reported previously,[5,6,8,23-25] indirect measures of renal arginine vasopressin activity do not accurately discriminate primary polydipsia from central diabetes insipidus, which has challenged the use of the indirect water-deprivation test as the diagnostic standard.[5,8,19] An essential limitation of urinary measures is the variably reduced maximal urinary concentration capacity inherent in all forms of chronic polyuria.[8] Moreover, enhanced renal sensitivity to even low levels of circulating arginine vasopressin in patients with central diabetes insipidus may complicate the interpretation of indirect tests.[26]

Our data confirm that additional measurements such as the basal plasma sodium level[27,28] or the urine-to-plasma osmolality ratio after fluid restriction[29] are of limited diagnostic value. In addition, in our study, the measurement of water-deprivation–stimulated copeptin levels did not improve diagnostic discrimination (73% of patients did not achieve hyperosmolality after 16 hours of fluid deprivation). Finally, although some clinical criteria (e.g., the presence of certain diseases,[30] additional clinical presentations,[2,31] and findings on MRI of the head[21,22,32]) are sometimes recommended to help in making specific diagnoses in patients with polyuria,[2] evidence to support their diagnostic value is insufficient and was not supported by our results.

Consequently, a test method that provides high diagnostic specificity, particularly for the critical distinction of primary polydipsia from central diabetes insipidus, is needed. After the early report on hypertonic saline administration by Hickey and Hare in 1944, in which indirect measures of renal function were used to detect

Table 3. Adverse Effects and Events and Test Burden.*

Variable	Water-Deprivation Test		Hypertonic Saline Infusion Test	
	no. (%)	*median VAS score (IQR)*	*no. (%)*	*median VAS score (IQR)*
Adverse effects				
Thirst	138 (98)	7 (5–9)	141 (100)	8 (6–9)
Vertigo	52 (39)	4 (2–5)	94 (68)	5 (3–7)
Headache	83 (63)	4 (2–5)	94 (67)	4 (2–6)
Nausea	47 (36)	2 (2–4)	69 (50)	4 (2–7)
Malaise	78 (59)	4 (3–6)	96 (69)	5 (3–7)
Adverse events				
Symptomatic overstimulation of plasma sodium	1 (<1)		2 (<1)	
Shivering	1 (<1)		3 (<1)	
Headache requiring pain medication	1 (<1)		0	
Diarrhea	0		1 (<1)	
Emesis after oral water intake	NA		1 (<1)	
Prolonged time until plasma sodium normalization after hypertonic saline infusion	NA		2 (<1)	
Hyponatremia due to excess water retention after administration of desmopressin	4 (<1)†		NA	
Test characteristics‡				
Symptom burden		6 (4–7)		5 (3–6)
Preference	49 (38)		79 (62)	

* A total of 141 patients underwent both tests. Scores on the visual-analogue scale (VAS) range from 0 to 10, with 0 indicating no symptoms and 10 indicating the most severe symptoms imaginable. NA denotes not applicable.
† One event led to hospitalization.
‡ The mean duration of the water-deprivation test was more than 20 hours, and the mean duration of the hypertonic saline infusion test was 3.1 hours.

the release of arginine vasopressin,[33] Zerbe and Robertson further developed the method by introducing direct measurement of plasma arginine vasopressin to differentiate primary polydipsia from diabetes insipidus.[8] Given the technical constraints of arginine vasopressin quantitation[5,11,34,35] and the highly variable functional sensitivity and specificity of the few assays approved for clinical use,[8,34] we designed our study to determine whether the measurement of copeptin is more reliable and easier to process and whether it can be standardized as a test that would detect the osmotic arginine vasopressin reserve.

The copeptin assay is designed to overcome the technical and functional caveats inherent in the arginine vasopressin assay,[8,12] and it appears to have the diagnostic potential not only to identify nephrogenic diabetes insipidus,[5,19,36] but also to distinguish central diabetes insipidus from primary polydipsia.[19] Building on our previous work, in which hypertonic saline infusion was initiated after fluid deprivation,[19] the current prospective validation study used a simplified protocol[16]: the test started with a saline bolus, which was followed by an infusion (at a rate according to each patient's body weight), thereby providing a more potent and prompt osmotic stimulus. This modified protocol attained a better outcome that validated the prespecified copeptin cutoff of 4.9 pmol per liter[19] and, excluding post hoc analysis, yielded the highest diagnostic accuracy for the entire population (96.5%), as well as for the critical distinction between mild forms of

arginine vasopressin deficiency and primary polydipsia (95.2%).

We note caveats with respect to the use of hypertonic saline infusion in the clinical evaluation of patients with polyuria. More adverse effects were reported with the hypertonic saline infusion test than with the water-deprivation test. The hypertonic saline infusion test required close monitoring of sodium levels to ascertain a diagnostically meaningful increase in plasma sodium within the hyperosmotic range[34,37] while preventing a marked increase, to which female patients appeared more vulnerable than male patients in this study.

Our study has limitations and strengths. One limitation is that there is no diagnostic standard for hypotonic polyuria. Here, we constructed criteria for reference diagnoses that were based on the full set of clinical data, the results of the indirect water-deprivation test, and the response of each patient to individual therapy at a 3-month follow-up visit, in accordance with clinical practice.[5,19] The simultaneous evaluation of the diagnostic accuracy of the indirect water-deprivation test and the use of those results in final decision making may have resulted in an incorporation bias. However, if this bias happened at all, it may have resulted in an overestimation of the diagnostic performance of the water-deprivation test. The strengths of the study involve the international multicenter design, the prospective validation of prespecified cutoff levels for hypertonic saline–stimulated copeptin release, and a relatively large sample size of patients with diabetes insipidus and primary polydipsia.

In conclusion, this prospective evaluation of patients with hypotonic polyuria validated hypertonic saline–stimulated copeptin measurement as a diagnostic method that appeared to be superior to the indirect water-deprivation test in distinguishing central diabetes insipidus from primary polydipsia.

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APPENDIX

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