# Utility of Copeptin Measurement in the Differential Diagnosis of Diabetes Insipidus

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**Abstract**
Given the different etiologies of Diabetes Insipidus disorders, there are major differences in treatment. For example, while central diabetes insipidus is mainly treated with exogenous AVP (desmopressin), patients with primary polydipsia are advised to slowly reduce their fluid intake. Therefore, a diagnostic test with high diagnostic accuracy is crucial to avoid wrong treatment decisions. While the standard water deprivation test as described for patient has been the diagnostic gold standard for decades despite its low diagnostic accuracy of only 70%, recent evaluations showed improved diagnostic accuracy for copeptin based tests. In addition to diagnosing diabetes insipidus in the outpatient clinic, copeptin measurement has also been proposed in the evaluation of postoperative central diabetes insipidus. While 1 study showed a high diagnostic accuracy of 100% for insulin-induced hypoglycemia-stimulated copeptin with a cut-off value of 4.75 pmol/L to detect central diabetes insipidus 3 months after pituitary surgery, the risks of this test outweigh its potential value.
**Keywords:** Copeptin, Diabetes Insipidus

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## Introduction

Given the different etiologies of Diabetes Insipidus, there are major differences in treatment. For example, while central diabetes insipidus is mainly treated with exogenous AVP (desmopressin), patients with primary polydipsia are advised to slowly reduce their fluid intake. Therefore, a diagnostic test with high diagnostic accuracy is crucial to avoid wrong treatment decisions. While the standard water deprivation test as described for patient has been the diagnostic gold standard for decades despite

its low diagnostic accuracy of only 70%, recent evaluations showed improved diagnostic accuracy for copeptin based tests **(1).**

The easiest etiology to diagnose is nephrogenic diabetes insipidus, since copeptin measurements of these patients revealed consistently high levels. In fact, it has been shown that using an unstimulated copeptin cut-off of >21.4 pmol/L had a 100% sensitivity and specificity to diagnose nephrogenic diabetes insipidus. Accordingly, no further evaluations than a random copeptin measurement are needed in these patients. Unfortunately, the distinction between central diabetes insipidus and primary polydipsia is not quite so straightforward because of the considerable overlap in baseline copeptin levels. In particular, distinguishing partial central diabetes insipidus from primary polydipsia is very challenging **(2).**

**Copeptin as a Predictive Marker for Central Diabetes Insipidus**

In addition to diagnosing diabetes insipidus in the outpatient clinic, copeptin measurement has also been proposed in the evaluation of postoperative central diabetes insipidus. While 1 study showed a high diagnostic accuracy of 100% for insulin-induced hypoglycemia-stimulated copeptin with a cut-off value of 4.75 pmol/L to detect central diabetes insipidus 3 months after pituitary surgery, the risks of this test outweigh its potential value **(3).**

Other studies used surgery itself as a stress test. In a study including 205 patients of which 49 had a postoperative diabetes insipidus, a copeptin level <2.5 pmol/L measured on the first postoperative day had a positive predictive level of 81% and specificity of 97%. Meanwhile, a copeptin level >30 pmol/L had a negative predictive value of 95% and sensitivity of 94% **(2).**

A second study examined the use of copeptin levels 1 hour after extubation after pituitary surgery. While a cut-off value below 4.2 pmol/L indicated permanent central diabetes insipidus, a value above 12.8 pmol/L was predictive of an unremarkable postoperative course. Since only 8 of the included 66 patients had central diabetes insipidus, however, these results should be confirmed in a larger cohort. In conclusion, copeptin-based tests are valuable diagnostic measures in the difficult distinction between diabetes insipidus and primary polydipsia **(4).**

**Differential diagnosis using copeptin measurement**

**Arginine infusion test**

Arginine infusion is known as a stimulator of the anterior pituitary and is used as a standard test in the evaluation of suspected growth hormone deficiency. Recent data showed that arginine is also a potent stimulator of the posterior pituitary. The study was divided into a physiological and diagnostic part, evaluating the effect of arginine infusion in healthy volunteers and in 96 patients with polyuria-polydipsia syndrome. Arginine infusion lead to a median copeptin increase from 5.2 pmol/l (interquartile range 3.3–10.9) to 9.8 pmol/ll (6.4–19.6) in the healthy volunteers. Post-hoc evaluation of arginine stimulation in patients showed that a copeptin level of 3.8 pmol/l 60 minutes after start of the infusion had a diagnostic accuracy of 93% to distinguish between central DI and PP **(5).**

The most common adverse effect was mild nausea, which occurred in 48% of the patients. Two patients were excluded from the main analysis because of vomiting, as vomiting can be a strong stimulator for AVP/copeptin release. If severe nausea or vomiting occurs during arginine infusion, test results can be used only if copeptin concentrations remain low. In all other cases a confirmatory test is recommended **(6).**

In summary, current data showed that copeptin-based diagnostic tests reliably differentiate between the different entities of the polyuria-polydipsia syndrome and have the potential to become the new gold standard tests. Of the two stimulation tests, the arginine infusion test would be preferable owing to its simple and safe test procedure, and would be an attractive test especially in children. However, the head-to-head comparison between the two tests and the validation of the proposed copeptin cutoff level has not yet been completed. Meanwhile, a stepwise approach for the diagnostic evaluation of diabetes insipidus is recommended **(7).**

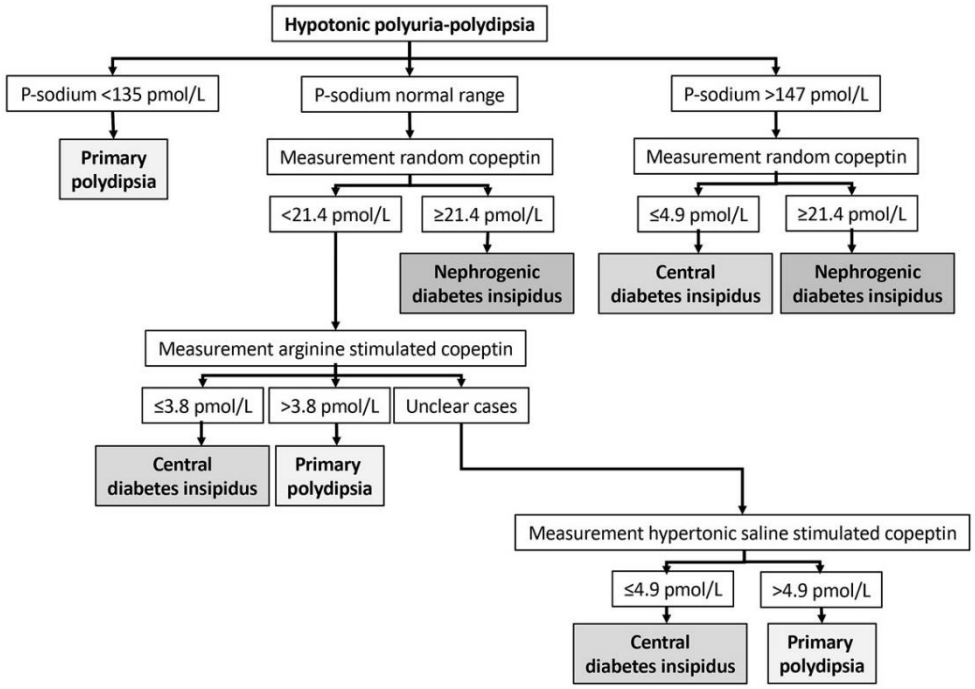


Figure (1): Copeptin-based diagnostic workflow for the differential diagnosis of polyuria-polydipsia syndrome. Unclear cases with the arginine stimulation test: in patients with severe nausea or vomiting test results have to be interpreted with care **(7).**

**Differential Diagnoses of Polyuria–Polydipsia Syndrome**

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 **(8).**

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 **(9).**

Direct measurement of plasma vasopressin (AVP) before and after a thirsting period has been recommended for better patient classification. Although direct AVP measurement led to a significantly better patient classification compared with urine osmolality measurement alone, 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, whereas a recent larger study found a less close association between the two parameters **(10).**

Second, reliable plasma AVP measurement is cumbersome due to multiple preanalytical and technical difficulties. In contrast, copeptin, the C-terminal glycoprotein moiety of pro-AVP, is a stable surrogate marker of AVP secretion **(11).**

Copeptin recently has been suggested to improve the differential diagnosis of DI, to mirror water deprivation and excess in healthy subjects, and to assess posterior pituitary function **(12).**

Plasma AVP investigation is not routinely used in the diagnostic pathway as AVP measurement is technically difficult for the hormone instability and the high in vitro thermolability. The AVP release leads to equimolar 1:1 ratio serum secretion of copeptin (CT-proAVP), a 39 amino acids protein-making part of preprovasopressin (pre-proAVP) precursor, characterized by in vitro stability; its measurement leads to reliable and fast results, not requiring pre-analytic laboratory processes. The correlation among AVP levels, serum osmolality and copeptin values is actually well known **(13).**

In adults, copeptin circadian rhythm is similar to the AVP rhythm, but both peaks and nadirs are delayed, likely for the copeptin longer half-time (86 minutes vs 44 minutes); this rhythm seems to be slightly blunted in nocturnal polyuria **(13).**

Recent studies in the pediatric age have explored the possibility to utilize copeptin also as a high-risk marker for community-acquired pulmonitis, septic shock, stroke and head trauma; in these studies, copeptin values in the control population were reported between 2.4 and 8.6 pmol/L **(14).**

The major challenge in PPS differential diagnosis still remains the right interpretation of the WDT and DDAVP test, overall for distinguishing PCDI (urinary osmolality after WDT and DDAVP test between 300 and 700 mOsm/kg) from PP. Thus, copeptin analysis can be a new tool to co-adjuvate the clinical decision and it might be included in the diagnostic pathway of the PPS. Up now, few literature data exist on its utilization in the PPS differential diagnosis and all derive from adult case series. Most reports conclude that the baseline plasma copeptin level is indeed useful in NDI distinction from other forms of polyuria-polydipsia, whereas its levels after WDT may be helpful in the differential diagnosis between CDI and PP **(13).**

With the development of the copeptin assay, an easy to measure, fast and reliable AVP surrogate with high ex vivo stability, the focus returned once more to the direct test method **(14).**

In a first study, Fenske et al. aimed to increase the diagnostic accuracy of the water deprivation test by combining it with copeptin measurement. In their cohort of 50 patients with polyuria polydipsia syndrome, baseline plasma copeptin levels >20 pmol/L diagnosed patients with nephrogenic DI, while levels <2.6 pmol/L after an overnight water deprivation test indicated central DI. A ratio of the Δplasma copeptin levels (before and after the water deprivation phase) to the plasma sodium level at the end of the test showed a high diagnostic accuracy of 94% in differentiating patients with central DI from patients with primary polydipsia **(15).**

In an evaluation of 55 patients with nephrogenic or central DI or primary polydipsia, we described copeptin further as a promising new tool for the diagnosis of polyuria polydipsia syndrome. This study confirmed in a larger patient number that patients with nephrogenic DI can be easily diagnosed by using a single baseline copeptin level of >21.4 pmol/L without prior thirsting. Baseline copeptin values in the other entities (i.e. central DI and primary polydipsia) however largely overlapped. Here, we showed that osmotically stimulated copeptin levels of >4.9 pmol/l differentiated patients with central DI from patients with primary polydipsia with a high diagnostic accuracy of 96%. Osmotic stimulation was performed using a standardized combined water deprivation followed by 3% saline infusion test aiming at an increase of plasma sodium levels above 147 mmol/L. The simultaneous evaluation of AVP measurement showed a lower diagnostic differentiation with a diagnostic accuracy of only 80% accuracy, which was especially low for differentiation between partial central DI and primary polydipsia (44%) **(16).**

Under this osmotic stimulation, 97% of the patients were correctly diagnosed using the copeptin cut-off level of >4.9 pmol/L. The diagnostic accuracy was similarly accurate in distinguishing patients with partial DI from patients with primary polydipsia with a correct diagnosis in 95%. Again, copeptin levels of all three included patients with nephrogenic DI exceeded the cut-off level of 21.4 pmol/L. Contrary to the study of Fenske described earlier, the proposed copeptin-sodium ratio did not improve the diagnostic accuracy of the water deprivation test, resulting in a diagnostic accuracy of only 44%. The proposed copeptin cut-off level of <2.6 pmol/L after an overnight water deprivation test to diagnose complete central DI had a diagnostic accuracy of 78%. The fact that the determination of copeptin after water deprivation alone does not lead to an improved diagnostic accuracy is most likely due to the inadequate osmotic stimulation. This observation is confirmed by the fact that most patients in the study did not reach hyperosmotic plasma sodium levels during the classical water deprivation test **(12).**

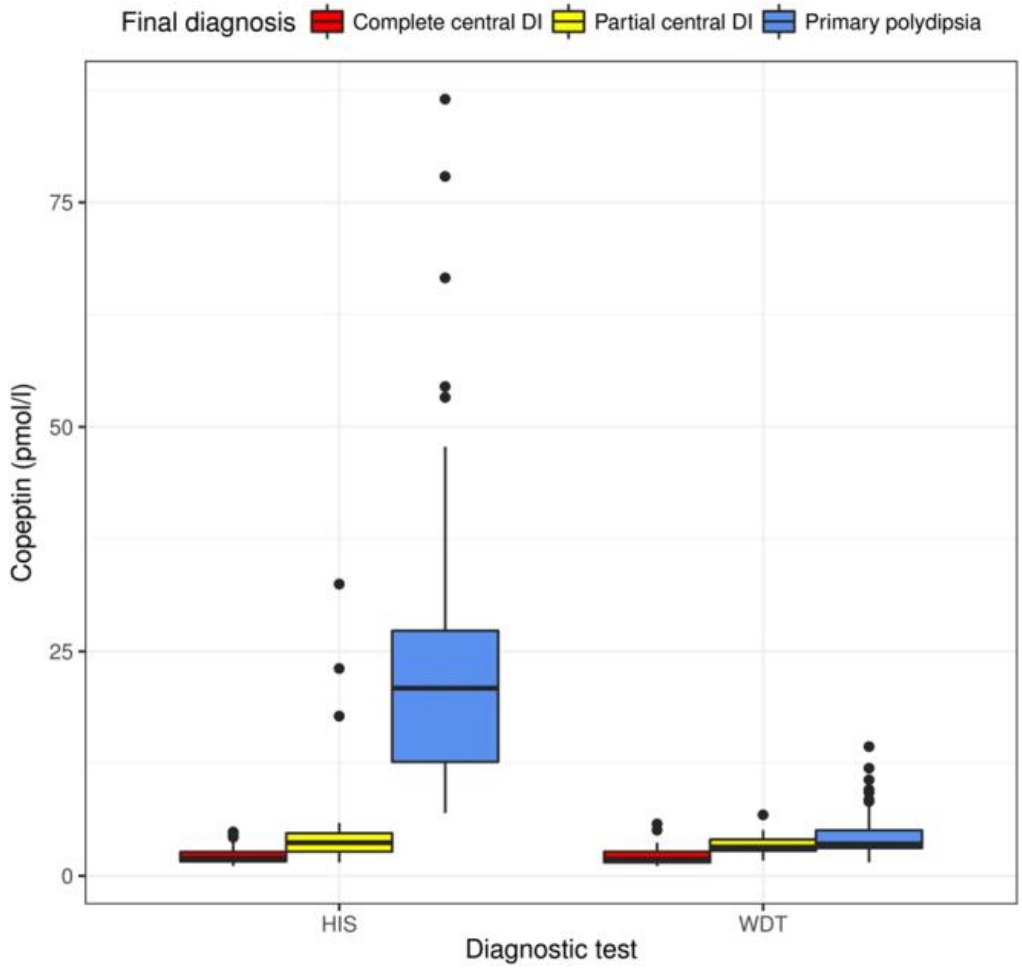


Figure (2): Stimulated copeptin levels in response to the hypertonic saline infusion and water deprivation test in patients with polyuria polydipsia syndrome. Shown are stimulated copeptin levels in response to the hypertonic saline infusion test (HIS) and water deprivation test (WDT) in patients with polyuria polydipsia syndrome that was caused by complete central diabetes insipidus (DI) or partial central diabetes insipidus as compared with primary polydipsia. 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 **(12).**

Accordingly, osmotic stimulation by hypertonic saline solution is needed to obtain reliable copeptin measurements. It is however important to note that hypertonic saline infusion requires close monitoring of sodium levels to ensure increase of plasma sodium levels into the hyperosmotic range while preventing osmotic overstimulation **(12).**

In settings where regular and rapid sodium monitoring is not possible, the hypertonic saline test should not be performed. Also, it might be prudent for clinical practice to aim at a plasma sodium level >147 mmol/L instead of 150 mmol/L. Rapid normalization of sodium levels after the osmotic stimulation is also crucial to guarantee the safety of the test **(12).**

Based on these results, it was concluded that the hypertonic saline test plus copeptin measurement might replace the classical water deprivation test in the future differential diagnosis of hypotonic polyuria **(17).**

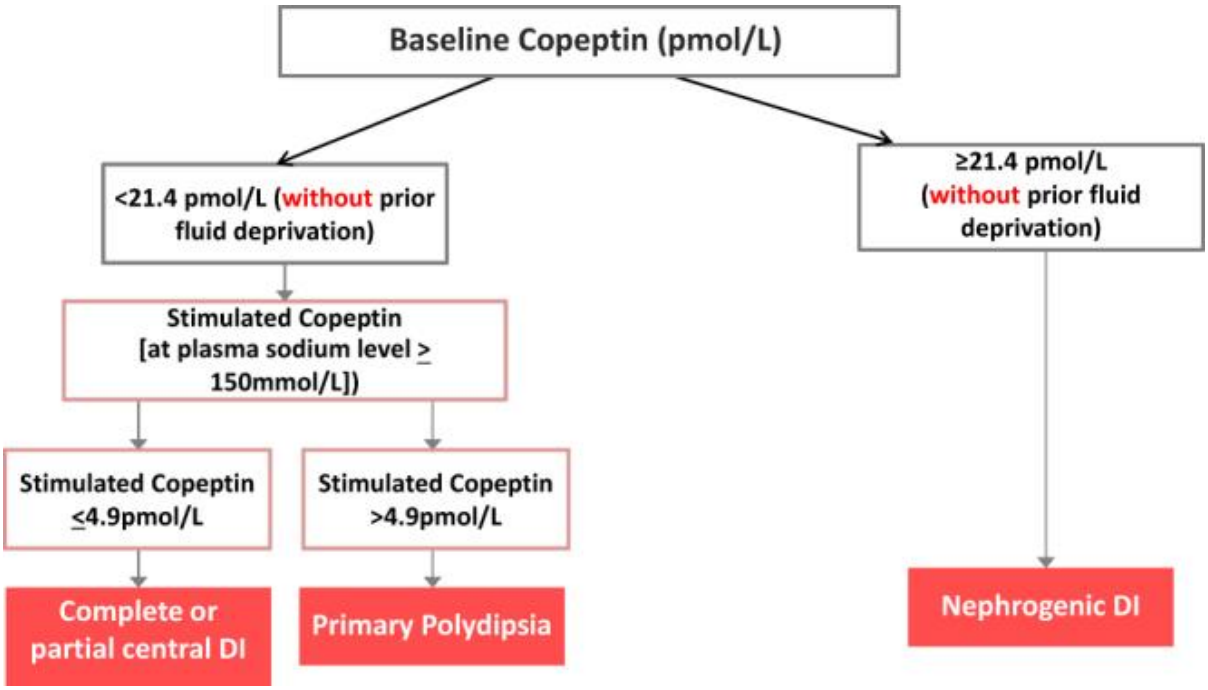


Figure (3): New algorithm for the differential diagnosis of polyuria polydipsia syndrome **(17).**

In conclusion, copeptin is a valuable and reliable diagnostic marker in the differential diagnosis of polyuria polydipsia syndrome. In a patient with unclear hypotonic polyuria and polydipsia, determination of basal copeptin levels is recommended to exclude nephrogenic DI. In patients with high suspicion of complete central DI, an overnight water deprivation test might confirm diagnosis provided urine osmolality remains below 300 mosm/kg and plasma sodium levels increase above 147 mmol/L. In all other patients, copeptin measurement after osmotic stimulation with 3% saline solution aiming at a plasma sodium level above 147 mmol/L is recommended. Importantly, close monitoring of plasma sodium levels is needed to ascertain a diagnostically meaningful increase in plasma sodium within the hyperosmotic range while preventing a marked increase, to which females appear to be more vulnerable than males **(18).**

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