# Diabetes Mellitus: New Ways to Make a Diagnose

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## Abstract

Primary polydipsia and Diabetes mellitus (DM), whether central or nephrogenic, must be distinguished. This distinction is essential because improper treatment can have harmful effects. The standard water deprivation test has been the "gold standard" for differential diagnosis for decades. However, this test has a number of limitations that make it less accurate overall for diagnosing problems. Additionally, the test takes 17 hours to complete and is time-consuming for patients. Additionally, patients with primary polydipsia and DI share many of the same clinical signs and symptoms as well as MRI characteristics. Although it was initially demonstrated that direct measurement of arginine vasopressin (AVP) upon osmotic stimulation could circumvent these limitations, the AVP assay's technical limitations prevented it from entering clinical practice. In line with the circulation's AVP concentrations, copeptin secretion is equimolar to AVP. We have demonstrated that patients with nephrogenic DI can be identified using copeptin even without prior fluid deprivation. A copeptin level of 4.9 pmol/L stimulated with hypertonic saline infusion differentiates between central DI and primary polydipsia with high diagnostic accuracy and is superior to the water deprivation test for the more difficult distinction between these two conditions. However, it is essential to note that the hypertonic saline test requires close and consistent sodium monitoring every 30 minutes, which is not always possible in all hospitals. Additionally, side effects are frequent. A non-osmotic stimulation test would therefore be beneficial. Because arginine significantly stimulates copeptin, it is a novel and undiscovered stimulus for this peptide. As a result, an even simpler and well-tolerated test was found to be arginine infusion with copeptin measurement; however, a head-to-head comparison is still lacking.

**Keywords:** Diabetes mellitus (DM); Polyuria Polydipsia Syndrome; Copeptin

## Introduction

The condition known as Diabetes mellitus (DM) is a part of the polyuria polydipsia syndrome. This syndrome is characterized by polydipsia of greater than 3 L per day and an output of >50 mL/kg body weight per 24 h of hypotonic urine (300 mOsm/kg H2O). Hypotonic polyuria can be caused by either primary polydipsia or central or nephrogenic DI, which are both possible diagnoses. Since different treatments work differently, it's important to have a good differential diagnosis. If the wrong treatment is used on a patient with primary polydipsia, for example, it could cause them to become intoxicated by water.

The conventional water deprivation test has been the "gold standard" for differential diagnosis for decades. However, due to a number of limitations, this test only has a diagnostic accuracy of around 70%. Arginine vasopressin (AVP) directly following hypertonic saline osmotic stimulation. The initial findings appeared to be promising, but sadly, the measurement of AVP did not enter clinical practice. This was primarily due to the technical limitations of the AVP assay and the fact that most reliable assays are not available commercially. As a result, the polyuria polydipsia syndrome's diagnosis and differential diagnosis will be discussed in this review [1].

## Polyuria Polydipsia Syndrome

Both primary polydipsia and central or nephrogenic DI are components of the polyuria polydipsia syndrome [2]. In clinical practice, it is common and getting more common, especially since many lifestyle programs say that drinking several liters of water a day is generally good for you.

Polydipsia typically follows hypotonic polyuria, which is caused by DI. The posterior pituitary does not produce an adequate amount of AVP in central DI. Lesions of the hypothalamic median eminence or the posterior pituitary are the most common causes of central DM. Trauma, pituitary surgery, neoplastic, vascular, autoimmune, infectious, or granulomatous diseases are the most common acquired causes. Up to 30% of patients undergoing pituitary surgery experience central DM, most of which is brief in nature. Postsurgical permanent DI occurs in 2–10 percent of patients. However, inherited forms of central DM are extremely uncommon. As previously stated, most of the time, the mechanisms of thirst remain intact, resulting in polydipsia. Lack of polydipsia can result in hyper osmolality and dehydration, both of which can have clinically serious complications [3-4]. On the other hand, levels of AVP are typically secreted in nephrogenic DM, but the kidneys resist the action of AVP. Acquisition of nephrogenic DM is also common, with drug-induced Nephrogenic DI being the most well-known cause. It is generally known that taking lithium causes Nephrogenic DM. Aquaporin 2 and AVP receptor 2 are two important proteins that can be altered through inheritance [5].

AVP secretion and renal function are unaffected in primary polydipsia. Overconsumption of fluids over an extended period is the primary issue. An abnormality in the thirst center, also known as dipsogenic DI, can occasionally cause it. However, it occurs much more frequently in various psychiatric Disorders (known as psychogenic polydipsia). Osmolality and AVP synthesis and release are stifled as a result of the excessive fluid intake. Free water is excreted as a result. Polydipsia can cause Reno-physiological adaptations over an extended period of time, such as compromising the renal medullary concentration gradient and down regulating aquaporin 2 channels in the kidneys. Urinary concentration capacity is hampered by both of these processes. Because causal treatment obviously varies and applying the wrong treatment can be clinically harmful and potentially life-threatening, a clear diagnostic Distinction between the various forms of DI and primary polydipsia is essential [6-7].

## Differential Diagnosis by Water Deprivation Test

The classic water deprivation test was the most common diagnostic tool for polyuria-polydipsia syndrome for a long time. This test identifies insufficient AVP secretion or effect based on the kidneys' insufficient concentration capacity over osmotic stimulation, which is reached after a prolonged thirsting period (typically 16 hours) and its response to exogenous AVP administration (Desmopressin). Miller et al.'s findings serve as the foundation for the conventional interpretation of the test. Five patients with primary polydipsia [8], two with Nephrogenic DI, and 29 with central DI (11 with partial DI) were evaluated in this study. Complete DI is diagnosed in patients whose urinary osmolality during the water deprivation test is below 300 mOsm/kg. If these patients' urinary osmolality rises by more than 50% following the administration of exogenous AVP, the final DIagnosis is complete central DI. On the other hand, if their urinary osmolality rises by less than 50% following the administration of exogenous AVP, the final DIagnosis is complete Nephrogenic

DI [9]. Patients with partial central DI or primary polydipsia are those whose urinary osmolalities increased to values between 300 and 800 mOsm/kg upon water deprivation. Patients with primary polydipsia saw a decrease of less than 9%, whereas patients with partial central DI saw an increase of more than 9% when exogenous AVP was administered [10]. These cutoff values, on the other hand, are derived from a single post hoc analysis of this small group of patients, and the raw data demonstrate a significant overlap in urinary osmolality levels. Using these criteria in the traditional water deprivation test had a Diagnostic accuracy of only about 70%, with a particularly low Diagnostic accuracy in patients with primary polydipsia, according to recent data aiming to validate these findings [11].

Direct test, in which plasma AVP is measured upon osmotic stimulation not only by thirsting, but also by stimulation with hypertonic saline infusion, to improve the Differential DIagnosis of the polyuria polydipsia syndrome. The physiological relationship between AVP release and plasma osmolality is then interpreted in relation to the normal area. Osmotically stimulated plasma AVP levels above the normal range are considered to be Nephrogenic DI, while levels below the normal range are considered to be central DI and levels within the normal range are considered to be primary polydipsia [12]. The findings demonstrated, to our satisfaction, that the conventional "indirect" water deprivation test's Diagnostic accuracy can be enhanced by directly measuring plasma AVP and interpreting urinary osmolality levels. However, despite these encouraging results, this direct test based on AVP measurement was not implemented into routine clinical practice. Sadly, recent studies using commercially available AVP assays failed to confirm these promising results. Particularly, a correct DIagnosis was only made in 38% of patients using commercially available assays, and Diagnostic accuracy was especially low when separating partial central Dizziness from primary polydipsia [13]. The issue is that there hasn't been a precise definition of the normal physiological relationship that describes plasma AVP as a function of osmotic activity for a long time. Although this is a crucial requirement for the use of Direct AVP measurement, the problem persists. Preanalytical instability is also high due to the AVP assay itself's technical limitations. It's important to note that there aren't many commercially available assays [14].

Therefore, new concepts for Differential Diagnosis are urgently needed.

### Copeptin: A New AVP Surrogate Marker

Copeptin, which is derived from the 164-amino acid precursor proteins Pre-Pro-Vasopressin, AVP, and Neurophysin II, was first found in the posterior pituitary of pigs in 1972 [18, 19]. Copeptin is a 39-amino acid glycosylated peptide with a leucine-rich core region and a molecular mass of approximately 5 kDa. It has a correlation index of r = 0.8 with plasma AVP. Notably, due to the AVP assay's complexity and methodological shortcomings, the correlation between plasma copeptin and plasma osmolality was even stronger than that between AVP and plasma osmolality. The same physiological stimuli, a relative increase in systemic osmolality and a relative decrease in arterial blood volume and pressure, regulate the release of plasma copeptin and plasma AVP into circulation, which are processed from the same precursor peptide. In a study involving 24 healthy adults, copeptin's surrogate properties for physiological AVP release due to osmotic regulation were first demonstrated. Plasma copeptin levels significantly increased following both fluid deprivation and hypertonic saline infusion. Additionally, there are non-osmotic stimuli for AVP and copeptin, such as nausea, hypovolemia, and hypotension, as well as unspecific somatic stress, such as in ischemic stroke, myocardial infarction, or pneumonia [15].

## Conclusion

In conclusion, the time-consuming and inaccurate water deprivation test has long been used to Diagnose DI and its Differential Diagnoses. Due to the AVP assay's technical limitations, the direct test with hypertonic saline infusion and AVP measurement did not become routine in clinical practice. Copeptin is a useful and reliable Diagnostic marker in the polyuria-polydipsia syndrome's Differential Diagnosis because it is a stable surrogate marker for AVP. Nephrogenic DI can be identified by measuring basal copeptin levels in hypotonic polyuric patients. After osmotic stimulation with 3% saline solution to achieve a plasma sodium level of 150mmol/L, copeptin measurement is recommended for all other patients. Importantly, careful monitoring of the sodium levels in the blood. The arginine stimulation test is an alternative that is even simpler and tolerates better without causing hypernatremia. A high stress-induced copeptin level immediately following pituitary surgery merely excludes later DI, whereas a low level strongly predicts later DI [16].

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