Diabetes Insipidus: Types, Diagnosis and Management

Jasmeen[1], *Phoebe* Vitubisgho Nyirenda[1], *Navneet* Khurana[1], *Rakhi* Mishra[2], *Jasmine* Chaudhary[3] and *Navneet* Duggal[1,*]

[1] School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar-Delhi G.T. Road, Phagwara, Punjab, India
[2] Noida Institute of Engineering & Technology, Greater Noida, Greater Noida, U.P, India
[3] MM College of Pharmacy, Maharishi Markandeshwar(Deemed to be University), Mullana, Ambala, Haryana, India

*Corresponding author: navneet.duggal@lpu.co.in, navneet.pharma@gmail.com

Abstract. Diabetes insipidus (DI) is an acquired or hereditary water imbalance disorder characterized by polydipsia and polyuria. It is a condition that involves the excretion of dilute urine in large volumes. The illness can strike at any age, with males and females have identical rates of occurrence of the disease. The two main mechanisms responsible for diabetes insipidus are either insufficient release or production of ADH (antidiuretic hormone) from the hypothalamus (central diabetes insipidus) or ADH resistance in which the kidneys are unable to respond to ADH (nephrogenic diabetes insipidus). Another form of DI is transient diabetes insipidus commonly known as gestational diabetes insipidus that occurs in the second/third trimester of pregnancy due to increased levels of placental vasopressinase that occurs progressively during pregnancy and increases metabolic clearance of vasopressin. The fourth type of DI is primary polydipsia, characterized by elevated levels of water intake that physiologically lower vasopressin and may be psychogenic, iatrogenic or dipsogenic. Signs and symptoms of DI often include water electrolyte-imbalance, excessive or severe thirst, frequent and excessive urination, fatigue, dehydration, and weight loss. Diabetes insipidus (DI) should be distinguished from primary polydipsia, and whether it is caused by a central, nephrogenic, or gestational cause. This distinction is critical since incorrect treatment can result in serious repercussions. Diagnosis of DI includes measurement of plasma sodium and osmolality, baseline copeptin, hypertonic saline stimulation and arginine stimulation test. The treatment for DI includes the use of drugs such as desmopressin, thiazide diuretics, indomethacin and amiloride.

1 Inroduction

Fundamental knowledge about kidney physiology can offer a better understanding about the functioning of the kidney and point us in the right direction for novel treatments [1]. The kidney plays a crucial role in maintaining water equilibrium by regulating both blood intravascular volume and osmolarity. Elevated plasma osmolality and hypovolemia stimulate carotid or aortic baroreceptors and hypothalamic osmoreceptors [2], respectively, to induce antidiuresis. The release of arginine vasopressin (AVP) or ADH is mainly responsible for the adjustment of water reabsorption [3]. Vasopressin, or AVP, is a peptide hormone that modulates plasma osmolality and extracellular fluid volume. The hypothalamus produces AVP which is stored in the posterior pituitary and plays a physiological role in the kidney via vasopressin V2 receptors present on collecting ducts and tubules [4,5]. Polydipsia (extreme thirst causing high levels of water or fluid intake) and polyuria (excretion of copious volumes of dilute urine of up to three liters in a day or twenty four hours) are the symptoms of diabetes insipidus [6,7]. DI is mainly classified as central or nephrogenic, depending on the underlying cause and may be of acquired or hereditary forms [8]. The other form of DI are primary polydipsia and gestational DI. DI is diagnosed on basis of measurement of plasma sodium and osmolality, baseline copeptin, hypertonic saline stimulation and arginine stimulation test. DI is frequently treated with administration of fluid in cases of dehydration and desmopressin is given to replace the hormone vasopressin which is absent in cases of central diabetes insipidus [9]. This review article aims at providing an overview on the different types of diabetes insipidus including its etiology or cause, diagnosis, treatment, and management of DI.

2 Epidemiology of diabetes insipidus

Diabetes insipidus is a rare condition with an incidence of 1:25,000. Hereditary diabetes insipidus accounts for less than 10% of diabetes insipidus cases [10]. Central diabetes insipidus is the most frequent form of diabetes insipidus, caused due to malfunction in the posterior portion of pituitary that causes a lack of ADH production and secretion. The acquired forms are far more prevalent in central DI than the hereditary variant [11]. Two genes are linked to nephrogenic diabetes insipidus (NDI). Pathogenic mutations in the arginine vasopressin receptor 2 in renal collecting duct cells produce X-linked recessive NDI in 90% of the cases. In the remaining 10%, pathogenic mutations cause NDI to be inherited in an autosomal recessive or dominant form[8]. Acquired form of NDI is more prevalent than the hereditary form. Long term lithium therapy is responsible for approximately 55% cases of NDI. Gestational DI affects about one in every 30,000 pregnancies [12], and individuals with gestational DI experience polyuria and polydipsia throughout pregnancy as a result of placental overproduction of vasopressinase[13].

3 Types of diabetes insipidus

Polyuria and polydipsia are common symptoms of diabetes insipidus. It is categorized into four types; with the two most common forms being central DI that results from reduced or impaired secretion of AVP [14] and nephrogenic DI caused by complete or partial sensitivity to AVP thereby leading to polyuria [15]. The other two types are gestational DI, which is caused by elevated levels of placental vasopressinase during the third trimester of pregnancy [16,17] and the fourth type being primary polydipsia in which lower physiological levels of AVP are caused by increased water uptake, as shown in fig. 1 [18,19].

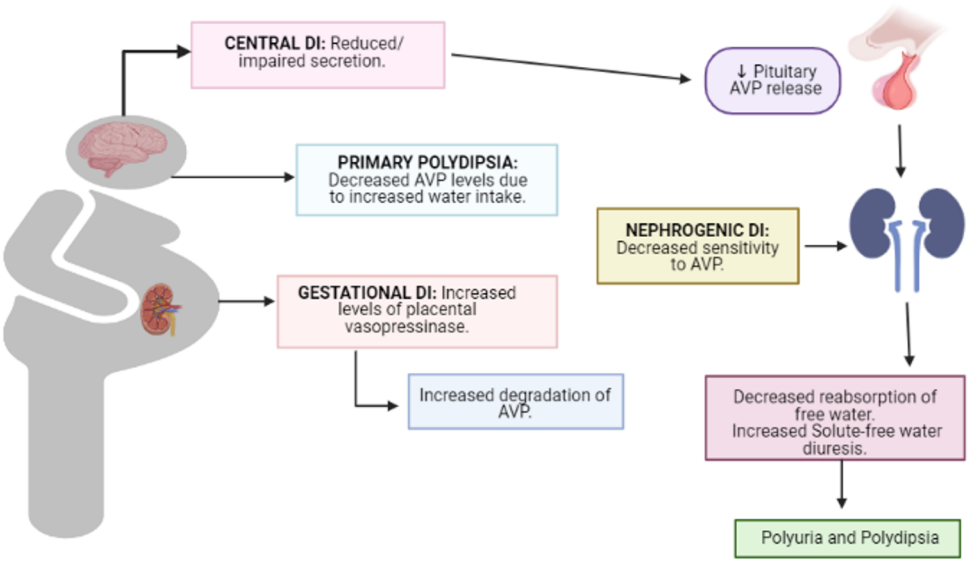


Fig. 1 Classification of diabetes insipidus

4 Diagnosis of various types of diabetes insipidus

Excessive urine (>50 ml/kg of body weight within 24 hour) and polydipsia (excessive drinking >3 litre/day) are symptoms of DI in adults. Due to the higher water content of their food, the normal urine volume in infants and children under the age of two years is slightly larger than the upper limit. If there is no pregnancy, gestational DI can be simply ruled out. It's crucial to distinguish polyuria from pollakiuria as a first diagnostic step, as well as rule out other possibilities like uncontrolled diabetes, hypercalcemia, or hypokalemia. 24-hour urine collection is required to establish the presence of hypotonic polyuria, once secondary causes have been ruled out. The polyuria–polydipsia syndrome causes can then be determined by measuring plasma sodium and osmolality levels. Decreased plasma osmolality (less than 280 mOsm/kg) and hyponatremia (plasma sodium less than 135 mmol/L) are both indicators of PP, whereas high plasma sodium (> 147

mmol/L) and/or plasma osmolality (>300 mOsm/kg) are indicators of diabetes insipidus. Nonetheless, the majority of people with polyuria-polydipsia will have normal sodium and osmolality levels, needing further diagnosis.

Since many years, classical water deprivation test was considered gold standard for differential diagnosis of diabetes insipidus. During a period of prolonged dehydration and after a subsequent injection of desmopressin, urine concentrating capacity is measured which is the basis of water deprivation test [20,21]. Recent research suggests that there are diagnostic limitations of the traditional water deprivation test. It has an overall 70% diagnostic accuracy and it has very poor accuracy in primary polydipsia patients, just 41. To get around these limitations, direct measurement of AVP has been suggested to enhance the differential diagnosis of diabetes insipidus. AVP concentrations were below the normal range in patients with central DI, nephrogenic patients with values above the normal range and primary polydipsia patients with AVP concentration within the normal range. However, due to substantial pre analytical instability, poor distinction between partial central DI and primary polydipsia, and lack of precise characterization of the normal physiological area defining the link between plasma AVP and osmolality, AVP measurement was not able to enter in clinical diagnosis of diabetes insipidus [22,23]. Therefore, in the present scenario, differential diagnosis of polyuria polydipsia syndrome is on the basis of measurement of copeptin, as shown in fig. 2**.**

Baseline Copeptin measurement

Copeptin was discovered in the posterior pituitary gland. Its concentrations are similar to those of AVP, but it is more stable and may be tested using commercially available assays [24]. Copeptin has the advantages of being stable at room temperature for several days, requiring no pre-analytical procedures, and being able to be quantified in 50ul serum or plasma within two hours [25]. There are now two certified assays: the original manual sandwich immunoluminometric assay and its replacement, the automated immunofluorescent assay available, which makes copeptin a possible biomarker for polyuria polydipsia syndrome differentiation[26]. Unstimulated copeptin levels over 21.4 pmol/L have hundred percent sensitivity and specificity for the confirmation of nephrogenic DI, i.e., copeptin levels collected before water deprivation or stimulation tests, as shown in fig. 2. While the baseline copeptin levels eliminate the requirement for additional nephrogenic DI testing, but will not be able be to distinguish central DI from primary polydipsia patients due to their substantial overlap. As a result, additional stimulation tests for those two groups are required.

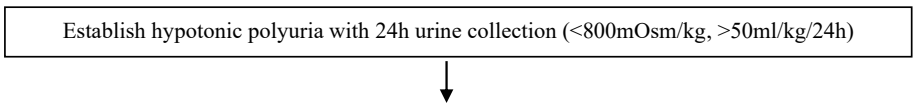
Hypertonic saline stimulation Test

To produce a plasma sodium level of ≥150 mmol/L, a 3 percent hypertonic saline solution was given (first in 250 ml bolus, then as an infusion at body weight-adapted rate). The benefit of the present test is the test length of two to three hours, which allows this test to be performed in an outpatient setting. Furthermore, although there is a higher risk of side effects such as malaise or vertigo, majority of the patients who underwent both the tests said that they are comfortable with the saline stimulation test compared to the classical water deprivation test. To avoid osmotic overstimulation and assure the test's safety, centers are required to monitor the increase in sodium levels accurately utilizing quick sodium readings [27].

After a hypertonic saline infusion, a plasma copeptin value less than 4.9 pmol/L suggests central DI (partial as well as total), but levels equal to or more than 4.9 pmol/L confirms primary polydipsia, as shown in fig. 2 [28].

Arginine stimulation Test

The amino acid arginine has recently been discovered to be another posterior pituitary stimulant. In clinical practice, arginine is employed as a standard test for activating growth hormone since it is a precursor of nitric oxide, an important signaling component of multiple endocrine mechanisms. A total of 92 healthy children and adults, as well as 96 individuals with diabetes insipidus, participated in a prospective study. The healthy volunteers' median copeptin levels increased from 5.2 pmol/L to 9.8 pmol/L after receiving an arginine infusion. Meanwhile, a copeptin level of 3.8 pmol/L measured 60 minutes after the start of infusion exhibited a diagnostic accuracy of 93 percent (sensitivity 92 percent, specificity 93 percent) in distinguishing the 38 central DI patients from the 58 primary polydipsia patients, as shown in fig. 2. The significance of the arginine infusion test is that it is simple, short and well-tolerated [25].



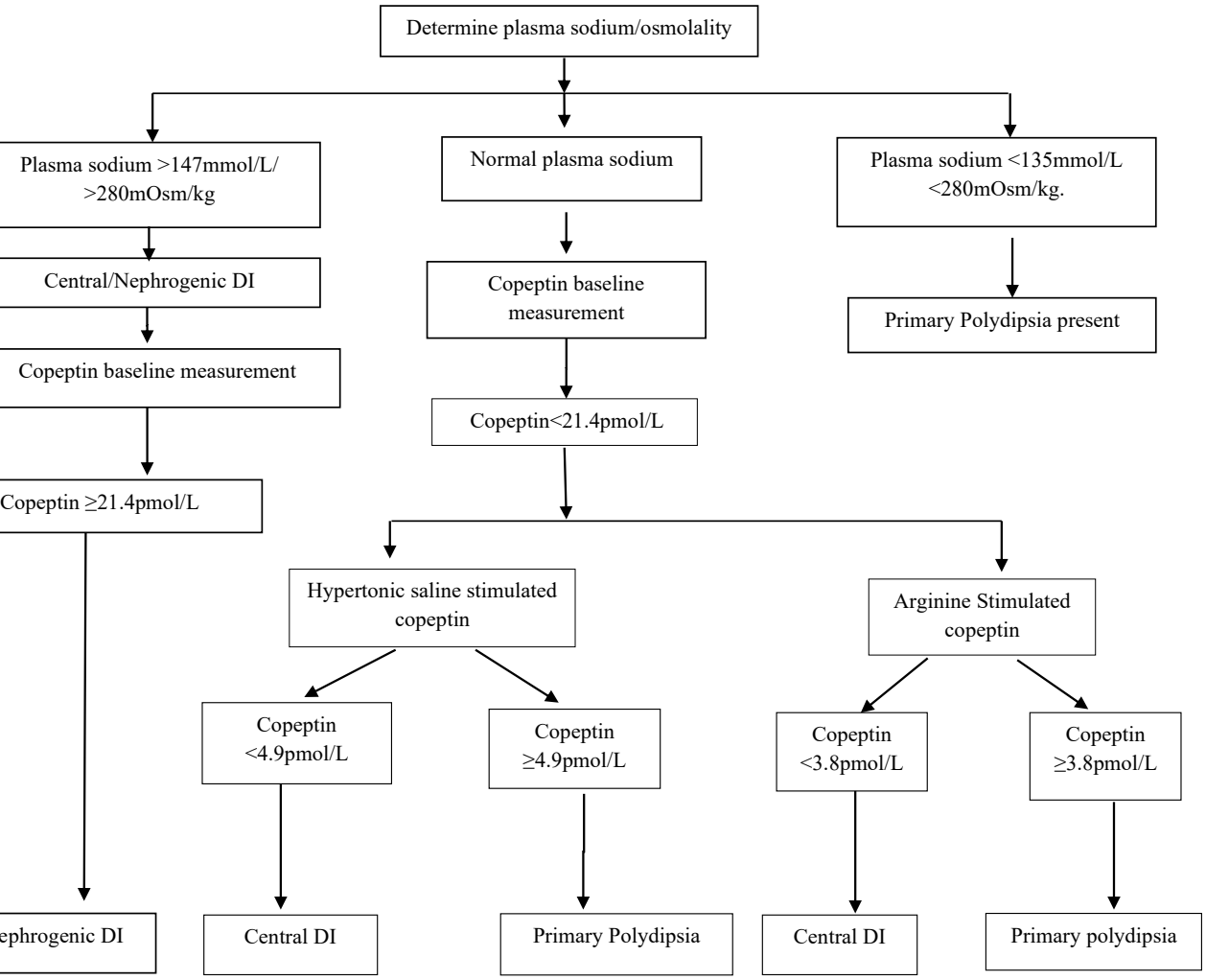


Fig. 2 Basic algorithmic method for diagnosis of diabetes insipidus using copeptin

5 Management and treatment

If the patient's thirst mechanism is intact, which means he or she is not receiving fluids for any reason and can drink water anytime they want, then management of diabetes insipidus is straightforward. Water balance can be achieved in this condition if the patient drinks adequate fluids. Patients with a reduced level of consciousness and impaired thirst mechanisms, as well as those receiving intravenous (IV) fluids, will need to alter IV fluids and medication on a regular basis to maintain proper hydration and sodium balance. These measures avoid hypernatremia dehydration. [29,30]. Dietary changes have been demonstrated to be beneficial in reducing solute burden on the kidneys, particularly in the case of NDI. It is recommended to eat a low-sodium, low-protein, high-calorie diet with a high calorie-to-solute ratio. Oral salt intake should be limited to 1 meq/kg/day, and protein consumption should be limited to 2 g/kg/day. Salt should be limited rather than proteins, which are required for growth [31]. The management of diabetes insipidus is critical to the patient's quality of life. Whether or not symptoms can be totally eased or treated is determined on the disorder's underlying source. There are a few first-line therapies for both central and nephrogenic DI that help in maintaining fluid balance. It is critical to have constant access to water to avoid becoming dehydrated too rapidly.

Nephrogenic DI

Patients taking lithium for bipolar illness account for the bulk of acquired cases of this rare condition [32]. Lithium therapy might lead to difficulties if it is used for an extended period. Even when lithium therapy has been stopped, prolonged lithium administration can cause irreversible nephrogenic diabetic insipidus [33,34]. The administration of DDAVP is ineffective because the primary problem is a nephron's insensitivity to ADH rather than a lack of ADH release [35]. Severe dehydration and hypernatremia can cause high morbidity and mortality in patients without proper treatment. Therefore, the aim of treatment for nephrogenic DI is to decrease urine output, normonatremia and sufficient fluid balance. These goals can be achieved through adequate water intake, low sodium diet and medications. The pharmacological treatment for nephrogenic DI includes thiazide diuretics, nonsteroidal anti-inflammatory drugs and amiloride, either prescribed alone or in combination [36].

Central DI

Central DI is primarily treated with DDAVP or AVP to replace absent AVP hormone due to decreased production of arginine vasopressin [37], with the route of administration being dependent on the clinical setting, whether acutely ill or hospitalized. Clofibrate, chlorpropamide and carbamazepine though ineffective and least preferred in comparison to DDAVP are also administered in Central DI treatment [38].

Primary Polydipsia

The best way to treat primary polydipsia is to employ behavioral therapy to reduce voluntary water consumption. However, because the patient is thirsty, this is challenging. The patient can be taught about the ailment, participate in group treatment, and learn to relax using biofeedback [39]. Support measures can also be created, like eating a well-balanced diet, preventing medicines that cause dry mouth, and monitoring weight to check retention of water [40]. Antipsychotic medications can also help to prevent hyponatremia and improve polydipsia behavior [41]. Clozapine, olanzapine, phenytoin, risperidone, bupropion, and propranolol are some of these medications. Primary polydipsia can produce hyponatremia, which can be managed with water restriction or a 3% saline infusion in more extreme cases [42,43].

Gestational DI

With low side effects profile, DDAVP used in gestational DI is delivered intranasally (recommended), orally, subcutaneously or intravenously. In most cases, DDAVP is started for the primary purpose of controlling nocturia. Increased needs from endogenous vasopressin metabolism by elevated placental vasopressinase levels may necessitate higher doses later in pregnancy. Hyponatremia symptoms, such as headaches, drowsiness and obtundation, must be closely monitored. If excessive water retention is suspected as a result of DDAVP overdosage, fluid restriction should be implemented right away. The use of DDAVP in pregnancy has been linked to a small increase in adverse effects for both the mother as well as the fetus, according to safety data. Due to a lack of controlled trials to give more detailed maternal and fetal safety evidence, DDAVP is still classified as pregnancy class B. The birth of neonate and delivery of placenta is the definitive therapy for gestational diabetes insipidus in pregnancy, in addition to fluid intake and DDAVP medication. Symptoms usually go away on their own 4–6 weeks after delivery [44]. Given that placental vasopressinase concentration will diminish in the first 4-6 weeks postpartum, doses of DDAVP can normally be completely stopped in the case of GDI following pregnancy. Lactation is safe for women who have been given DDAVP after giving birth because very less DDAVP enters the breast milk. After four to six weeks of child birth treatment is often discontinued and reinvestigated if diabetes insipidus recurs [45].

6 Conclusion

The repercussions of untreated DI can be extremely stressful for the patient and have a poor influence on their quality of life, as a result, adequate treatment is required. Only a comprehensive diagnosis of DI can lead to effective treatment. The water deprivation was previously used as the gold standard for diagnosis now being replaced by the use of copeptin. Copeptin has proven to be a promising biomarker in the diagnosis of DI and can lead to stable and easy diagnosis with a greater accuracy. The new gold standard was proposed to be a hypertonic saline infusion test which showed improved diagnostic accuracy. Depending on the underlying cause and type, diabetes insipidus can be treated with drugs such as amiloride, indomethacin and thiazide diuretics, however desmopressin still remains the choice of drug for central DI.

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