Salt and Water: A Review of Hypernatremia

Niralee Patel, Dhwanil Patel, Samira S. Farouk, and Joshua L. Rein

Serum sodium disorders are generally a marker of water balance in the body. Thus, hypernatremia is most often caused by an overall deficit of total body water. Other unique circumstances may lead to excess salt, without an impact on the body's total water volume. Hypernatremia is commonly acquired in both the hospital and community. As hypernatremia is associated with increased morbidity and mortality, treatment should be initiated promptly. In this review, we will discuss the pathophysiology and management of the main types of hypernatremia, which can be categorized as either a loss of water or gain of sodium that can be mediated by renal or extrarenal mechanisms.

Key Word: Hypernatremia, Sodium, Water, Salt, Vasopressin, AQP2, Diabetes insipidus, Kidney, Renal

Abnormalities in serum sodium concentration correlate with the overall hydration status: too much or too little water in the intravascular space. In a normal physiologic state, serum sodium concentration is maintained within a tight range of 135-145 mEq/L in the face of large variations in salt and water intake and output. Hypernatremia is defined as an increase in serum sodium concentration above 145 mEq/L, indicative of a hyperosmolar state due to a relative water deficit that is out of proportion to the sodium content in the body. Hypernatremia occurs in approximately 1%-3% of hospitalized patients[1,2] and is associated with increased morbidity and mortality.[3-6] Hypernatremia develops most commonly due to loss of water, although occasionally can be attributed to excess gain of sodium, and is further categorized by volume status, which is a reflection of both total body sodium and water (Fig 1).

THE PHYSIOLOGY OF OSMOTIC HOMEOSTASIS

Increases in serum osmolality are sensed by osmosensory neurons along the third ventricle of the brain, in the organum vasculosum lamina terminalis and the subfornical organ. Neurons in these regions stimulate both thirst and the production of hypothalamic preprovasopressin in magnocellular neuron bodies of the paraventricular nucleus and supraoptic nucleus. Preprovasopressin undergoes enzymatic posttranslational cleavage into arginine vasopressin (AVP), neurophysin II, and copeptin, which are copackaged in vesicles during axonal transport toward neuronal terminals in the posterior pituitary. AVP is stored in these neurosecretory vesicles and released into the bloodstream upon stimulation of magnocellular neurons in response to changes in extracellular osmolality (Fig 2). Circulating AVP activates the vasopressin 2 receptor (V2R) on the basolateral membrane of principal cells (PCs) in the kidney collecting duct (CD) to stimulate aquaporin 2 (AQP2) insertion into the apical membrane. AQP2 insertion allows for the transcellular reabsorption of water, driven by an osmotic gradient between the tubule lumen and interstitium (Fig 3). If the above mechanisms are intact, hypernatremia should not develop unless there is impaired access to free water or significant renal or extrarenal free water losses that are not replaced quickly.

Acute vs Chronic Hypernatremia

Acute hypernatremia is defined as being present for less than 48 hours, while chronic hypernatremia has been present (or presumed to be) for greater than 48 hours. Consequences of acute changes in extracellular osmolality primarily affect the central nervous system. In hyperosmolar states, water is drawn out of the intracellular space, leading to cell shrinkage. Cell mechanosensors detect acute cell shrinkage and implement mechanisms to stimulate sodium, potassium, and chloride influx and restore cell volume in a process called regulatory volume increase. During hypoosmolar states, cells swell, and compensatory mechanisms release osmolytes, primarily potassium, chloride, and taurine, leading to compensatory cell shrinkage back to normal in a process called regulatory volume decrease. Acute increases in serum sodium cause neuronal cell shrinkage and the potential for demyelination. In this situation, treatment should occur rapidly to prevent severe neurological complications. Conversely, rapid decreases in extracellular osmolality cause neuronal cell swelling within the cranium, and thus, increased intracranial pressure (ICP) can cause brain herniation and death.[7]

Unlike hyponatremia, there are currently no established guidelines for correction rates of hypernatremia. Chronic hypernatremia correction has been recommended by experts to be a reduction in the serum sodium level at a rate less than 0.5 mEq/L/h (12 mEq/d) to diminish the risk of possible cerebral edema.[7,8] Although there is a concern for overcorrection and neurological impairment in infants when raising the serum sodium more than 0.5 mEq/L/h,[9] the risk of neurological complications from rapid overcorrection of hypernatremia in adults remains theoretical. A recent large retrospective study of patients with hospital- or community-acquired chronic hypernatremia revealed no adverse neurological outcomes and

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similar mortality rates among patients with a fast sodium correction rate (greater than 0.5 mEq/L/h) compared to a slow correction rate of less than 0.5 mEq/L/h.[10] Of note, there were no cases of cerebral edema or seizure among patients with the fast correction rate. Retrospective studies have actually shown that slow correction of hypernatremia may be associated with a higher mortality.[6,11] A follow-up randomized control trial to the SALSA (Efficacy and Safety of Rapid Intermittent Correction Compared With Slow Continuous Correction With Hypertonic Saline in Patients With Moderately Severe or Severe Symptomatic Severe Hyponatremia) trial, is comparing rapid intermittent bolus to slow continuous infusion of 5% dextrose water in patients with severe hypernatremia.[12]

The total-body free water deficit can be calculated to determine the estimated volume of water needed to return elevated sodium levels to normal.[8]

Free water deficit = total body water × ([serum Na/140] − 1)

Total body water (L) is estimated by multiplying weight in kg by 0.6 for men and by 0.5 for women.

This formula is an overall estimate, as it does not account for ongoing water losses. In fact, equations do not always perform well among critically ill patients.[13] Therefore, the serum sodium concentration needs to be monitored frequently to guide treatment. Once the losses are calculated, water can be administered enterally and/or parenterally.

CLINICAL SUMMARY

- Hypernatremia occurs from either a loss of water or gain of sodium that can be mediated by renal or extrarenal mechanisms.
- Disorders of extrarenal water losses with preserved vasopressin release and function are associated with appropriately concentrated urine with high osmolality compared to disorders of renal water losses that are associated with an "inappropriately" low urine osmolality.

HYPERNATREMIA FROM EXTRARENAL WATER LOSS

Water leaves the body through the respiratory, integumentary, genitourinary, and gastrointestinal systems that are in contact with the external environment. Hypotonic fluid losses will raise the serum sodium concentration if water losses are not replaced despite the body's response to maximally conserve water through the action of AVP. Patients with significant hypotonic fluid losses may be hypovolemic, with a low fractional excretion of sodium, indicative of sodium avidity.[14,15] Sweat, despite its "salty" taste, is hypotonic compared to plasma (sweat 120 mOsm/kg vs. blood 285 mOsm/kg).[16] Adults can lose half a liter of sweat per day, and this volume increases significantly with warmer weather, fevers, and strenuous physical activity.[14,17] Hypotonic gastrointestinal fluid losses (eg, vomiting, diarrhea, drainage of gastric secretions) will lead to hypernatremia if water losses are not restored. Respiratory secretions and exhaled water vapor contribute significantly to insensible losses in people with high minute ventilation.[18] Hypernatremia is a common complication among burn victims from evaporative water loss through damaged skin.[19] The most common cause of hypernatremia is inadequate water intake in the setting of excess water losses, which is often seen in critically ill patients or those who have neurological or physical deficits that prevent free access to water.[3] Those unable to maintain free water intake in the setting of significant hypotonic volume losses or have hypodipsia are also vulnerable.[16] Disorders of extrarenal water losses and preserved AVP release and function are associated with appropriately concentrated urine with high osmolality (UOsm) compared with disorders of renal water losses that are associated with an "inappropriately" low UOsm.

HYPERNATREMIA FROM RENAL WATER LOSS

Defects in water conservation by the kidney can lead to excess free water lost in the urine. Renal water losses can be distinguished by extrarenal water losses by an inappropriately low UOsm, despite extracellular hyperosmolarity.

Diabetes Insipidus

Diabetes insipidus (DI) is characterized by hypotonic polyuria with secondary polydipsia due to *impaired AVP secretion* from the posterior pituitary (central DI), *AVP resistance* in the kidney (nephrogenic DI),[20] or *increased AVP degradation* by placenta-derived vasopressinase during pregnancy (gestational DI).[21] Defects in AVP secretion or action are most commonly acquired as a result of various injuries or diseases but can also be idiopathic or genetic in origin.[22] Depending on the extent of neuronal damage or protein loss of function, DI can be categorized as "complete" when there is 100% dysfunction of the pathway or "partial" when some function is retained, although not enough to maintain a normal serum sodium level. Partial DI may not be clinically apparent and may be difficult to diagnose without formal water deprivation testing (Fig 4). Similar to the treatment of hypernatremia from other etiologies, treatment of hypernatremia from DI involves water replacement and, in acquired cases, correcting the underlying condition. Both complete and partial DI are likely to present with low UOsm in the setting of hypernatremia, indicative of abnormal AVP activity.

Central DI

Central DI results from any abnormality in the hypothalamic-neurohypophyseal system that ultimately leads to reduced or no AVP secretion from the posterior pituitary (Fig 2).[23] Here, the urine concentrating ability of the kidney is intact, and exogenous administration of AVP corrects the disorder. As AVP has a relatively short half-life, its synthetic analog desmopressin (DDAVP) is often used for both the diagnosis and treatment of central DI.[24] DDAVP has a half-life around 3 hours and multiple routes of administration (intranasal, oral, and parenteral).[25]

Acquired causes of central DI can occur as a result of disruption or physical destruction of vasopressinergic neurons (eg, postoperative injury, head trauma, or anoxic

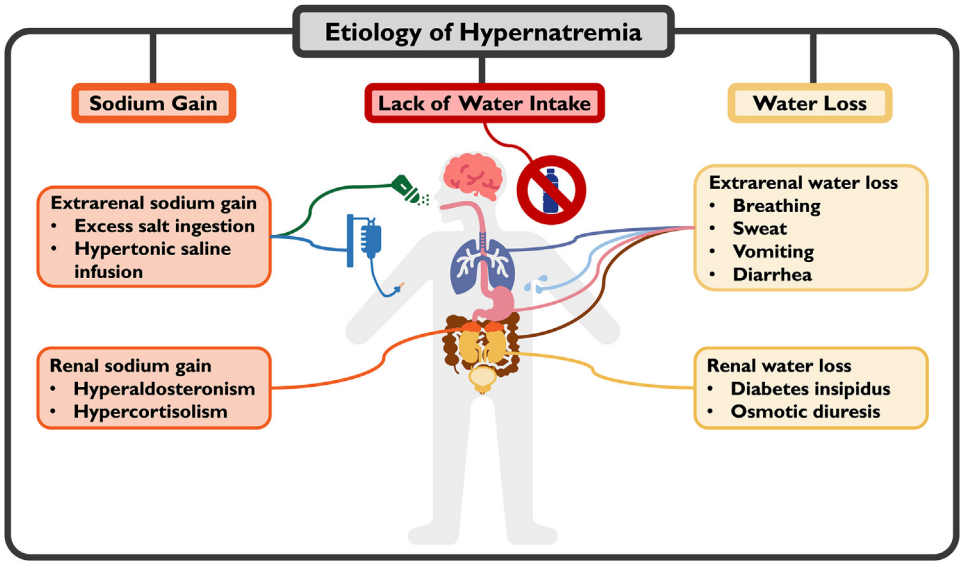

Figure 1. Hypernatremia can develop from renal and extrarenal sodium gains and/or water loss that are out of proportion to water intake. Water loss occurs through the respiratory, integumentary, genitourinary, and gastrointestinal systems that are in contact with the external environment. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

brain injury), infiltrative diseases (eg, neurosarcoidosis, Langerhans cell histiocytosis), external compression (eg, primary brain tumors, metastatic lesions), infections (eg, meningitis, encephalitis), inflammatory/autoimmune conditions (eg, lymphocytic, xanthomatous, IgG4-related hypophysitis), and drugs (eg, checkpoint inhibitors, ethanol). Hereditary central DI can be caused by an autosomal dominant mutation in the *AVP* gene that leads to defective protein function. As a valuable preclinical animal model, the Brattleboro rat has naturally developed hereditary central DI because of a single amino acid deletion causing a frameshift mutation in *AVP* and the loss of a normal stop codon.[26] AVP mRNA is able to be made but leads to the synthesis of dysfunctional protein that gets trapped in the endoplasmic reticulum, thus a lack of secreted AVP.[27]

Nephrogenic DI

Nephrogenic DI can be inherited or acquired through defects or impairments in V2R signaling and/or AQP2 function. Greater than 90% of inherited forms are X-linked nephrogenic DI from mutations in *AVPR2*, while mutations in *AQP2* account for the remaining cases. Acquired causes of nephrogenic DI can be secondary to tubular dysfunction or damage to the kidney medulla from medications (eg, lithium, cisplatin, demeclocycline), electrolyte disorders (eg, hypokalemia, hypercalcemia), or hematologic disorders (eg, multiple myeloma, amyloidosis, sickle cell disease).

Lithium has been successfully used for the treatment of bipolar disorder for decades. However, nephrogenic DI can occur in 20%-30% of people taking lithium, making it the most common cause of acquired nephrogenic DI.[28] Lithium follows similar transport pathways as sodium in the kidney. Within the PC, lithium blocks AQP2 production and downregulates V2R. Lithium-induced nephrogenic DI is usually reversible after drug withdrawal. However, for some people, it may take several months or years for the kidney to regain its urinary concentrating ability, while very few patients have irreversible nephrogenic DI, even with discontinuation of lithium. Tolvaptan, a V2R antagonist, is used for the treatment of hyponatremia and polycystic kidney disease and can lead to hypernatremia, even in low doses, especially among patients who do not have access to water.[29]

Nephrogenic DI is more difficult to treat than central DI because the kidney has some degree of resistance to AVP analogs. However, high doses may elicit at least a partial response and improve polyuria in some patients. Although a diuretic, thiazides with a low-sodium diet can increase urine concentration and decrease urine volume by inducing a mild hypovolemia with activation of the renin-angiotensin-aldosterone system to increase sodium and water reabsorption in the proximal tubule, thus reducing the volume delivered to the distal nephron.[30] Amiloride, a potassium-sparing diuretic, blocks the epithelial sodium channel ENaC, which is an entry point for lithium into the PC.[31,32] Therefore, amiloride has been shown to counteract lithium toxicity in PCs and reduce polyuria by preventing the downregulation of AQP2 channels.[33] A combination of both thiazides and amiloride has been studied in those with congenital DI for their synergistic effects to decrease polyuria.[34] Acetazolamide has also been shown to improve the urine-concentrating ability and reduce polyuria in treatment-resistant lithium-induced nephrogenic DI.[35] Nonsteroidal anti-inflammatory drugs, such as indomethacin, inhibit prostaglandin synthesis and have the ability to concentrate the urine by decreasing the glomerular filtration rate and increasing urinary sodium and urea, thus increasing

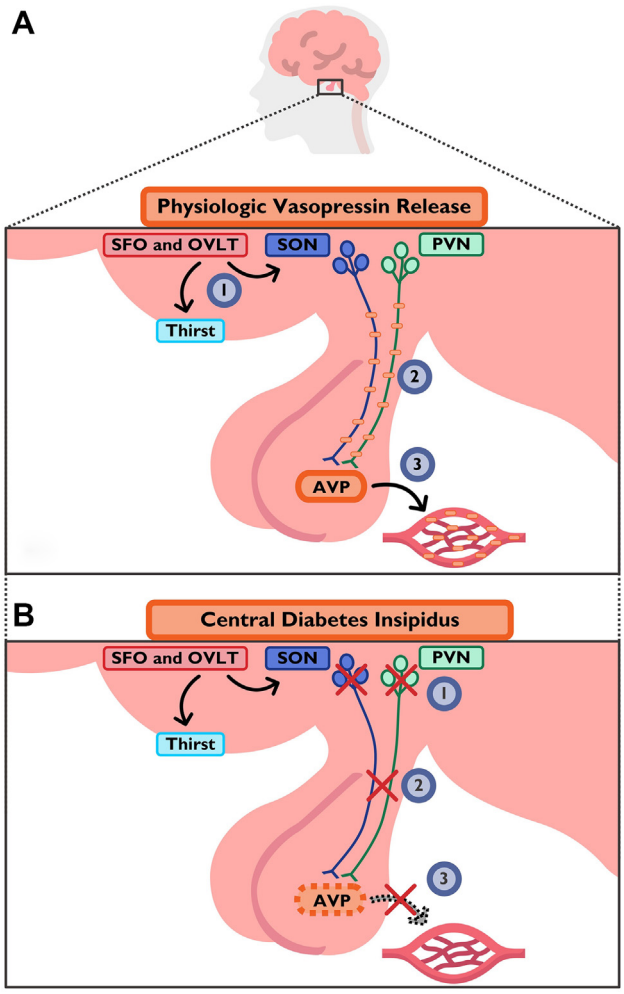

Figure 2. (A) Physiologic release of vasopressin. (a.1) Osmosensory neurons in the subfornical organ (SFO) and organum vasculosum lamina terminalis (OVLT) are activated by increased serum osmolality causing thirst stimulation and hypothalamic production of preprovasopressin. (a.2) Preprovasopressin undergoes cleavage to form vasopressin, copeptin, and neurophysin II, which are copackaged in vesicles during axonal transport. (a.3) Vasopressin is released from axon terminals into the systemic bloodstream. (B) Central diabetes insipidus. (b.1, b.2) Acquired injury to the cell bodies of neurons that produce PPV in the supraoptic nucleus (SON) and paraventricular nucleus (PVN), or to neuronal axons in the pituitary stalk, will lead to decreased or no production of vasopressin. (b.3) Defects in vesicle exocytosis at the axon terminal impair vasopressin secretion into the systemic circulation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

UOsm.[36] However, the overuse of nonsteroidal anti-inflammatory drugs can have its own adverse effects on kidney function and need to be used cautiously.

Gestational DI

Extracellular volume expansion in pregnancy is mediated in part by increased AVP secretion in response to systemic vasodilatation and a "reset osmostat." This response leads to water reabsorption by the kidney and a decrease in extracellular osmolality. However, placental vasopressinase is produced around week 7 and can degrade endogenous AVP.[21] Vasopressinase levels increase with placental growth and, thus, reach maximal levels around the late second and early third trimester. Peak vasopressinase levels are associated with a decrease in circulating AVP by 80%-85% and contribute to the common symptoms of pregnancy-related polyuria and polydipsia. DDAVP is resistant to vasopressinase degradation because of a deaminated N-terminus and, thus, is an effective treatment for severe cases of gestational DI. Vasopressinase levels progressively decrease over the 4-6 weeks following delivery.[21]

THE WATER DEPRIVATION TEST, PLASMA AVP, AND COPEPTIN

In the evaluation of polyuria, the water deprivation test (Fig 4) can be used to distinguish DI from other causes of polyuria, such as primary polydipsia. This test compares the UOsm before and after a period of water deprivation, with or without the administration of hypertonic saline. Administration of DDAVP can assess the efficacy of AQP2 insertion and function and, thus, the concentrating ability of the CD. In central DI, DDAVP administration will significantly increase water reabsorption in the kidney. Urine will remain dilute or improve only slightly after DDAVP administration in those with nephrogenic DI.

Although plasma AVP can be measured, results may be inaccurate and challenging to interpret secondary to its short half-life ($T_{1/2}$ 5-10 minutes).[37] Thus, plasma copeptin, the 39 amino acid C-terminal fragment of PPV with a longer half-life, can be reliably measured as a surrogate for AVP. In order to distinguish central DI from primary polydipsia, plasma copeptin levels can be measured after a water deprivation (17-hour fluid restriction) or an infusion of hypertonic saline (250 mL bolus of 3% saline followed by a rate of 0.15 mL/kg/min for 2 hours).[38] Plasma copeptin levels increase after water deprivation and hypertonic saline administration in patients with primary polydipsia and not in central DI, improving the diagnostic accuracy as compared to urine osmolality measurements. However, both water deprivation and hypertonic saline administration have the potential to cause hypernatremia and hypervolemia leading to adverse effects. Thus, the infusion of arginine, which acts centrally to stimulate production of several hormones including AVP in the posterior pituitary, is an attractive alternative.[39] Arginine infusion (0.5 g/kg mixed in 500 mL of normal saline over 30 minutes) resulted in increases in plasma copeptin in patients with primary polydipsia and not in central DI. The measurement of serum copeptin is promising but is not readily available in many clinical laboratories.

Osmotic Diuresis

Hypernatremia can occur from urinary water losses induced by excess solutes or osmotic diuretics if water intake is inadequate.[40] Although urinary free water losses are usually associated with a low UOsm, hypotonic fluid loss induced

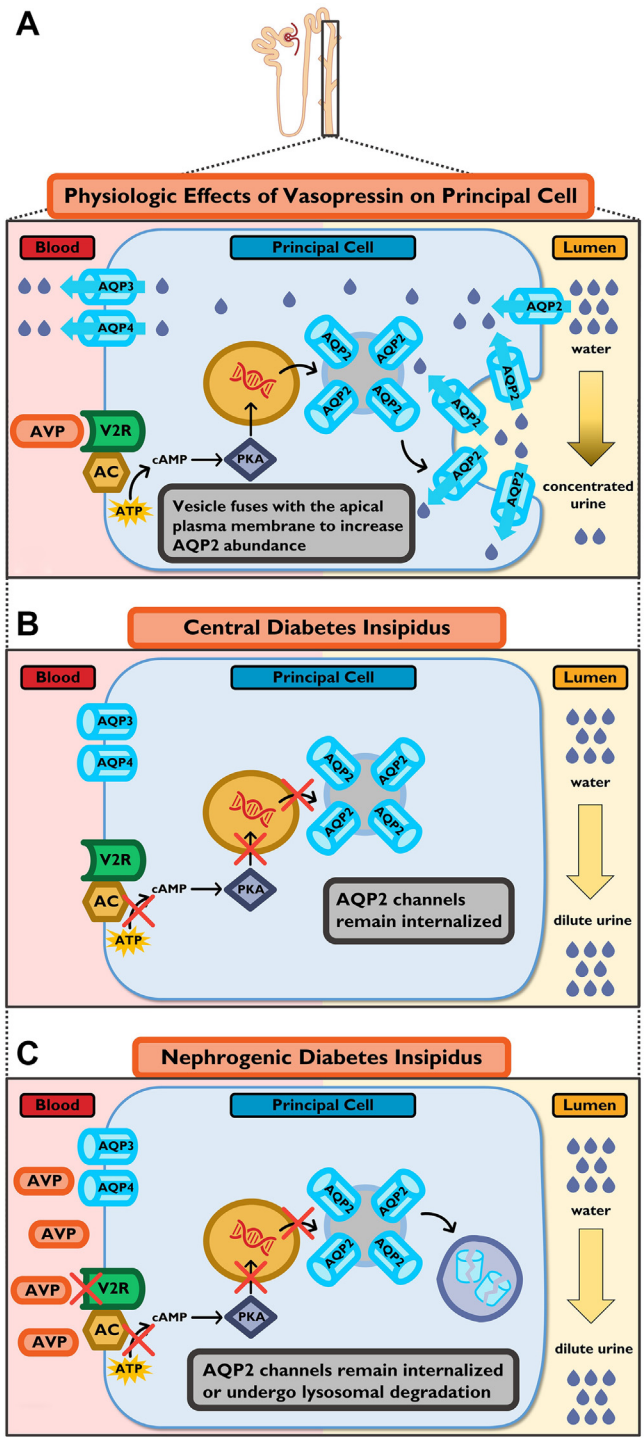

Figure 3. (A) Physiologic effects of vasopressin on principal cells. Vasopressin stimulates vasopressin receptor type 2 (V2R) that activates intracellular signaling by activating adenylate cyclase to increase intracellular cyclic adenosine monophosphate (cAMP). cAMP promotes protein kinase A (PKA)-mediated aquaporin 2 (AQP2) gene transcription. Subsequently intracellular vesicles that store AQP2 channels are fused with the apical membrane allowing for transcellular water reabsorption. (B) Central diabetes insipidus. Due to a defect in the hypothalamic-neurohypophyseal system, there is no circulating vasopressin. V2R remains inactive from the lack of vasopressin, and AQP2 stays internalized in intracellular vesicles, leading to decreased water reabsorption and the production of hypotonic polyuria. (C) Nephrogenic diabetes insipidus. Although vasopressin is abundant in the systemic circulation, defective V2R is unable to be activated that would have promoted apical translocation of AQP2 channels. Additionally, inherited or acquired defects can increase AQP2 lysosomal degradation, and the lack of functional AQP2 channels on the apical plasma membrane means that water is unable to be reabsorbed. Abbreviation: AC, adenylate cyclase; ATP, adenosine triphosphate. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

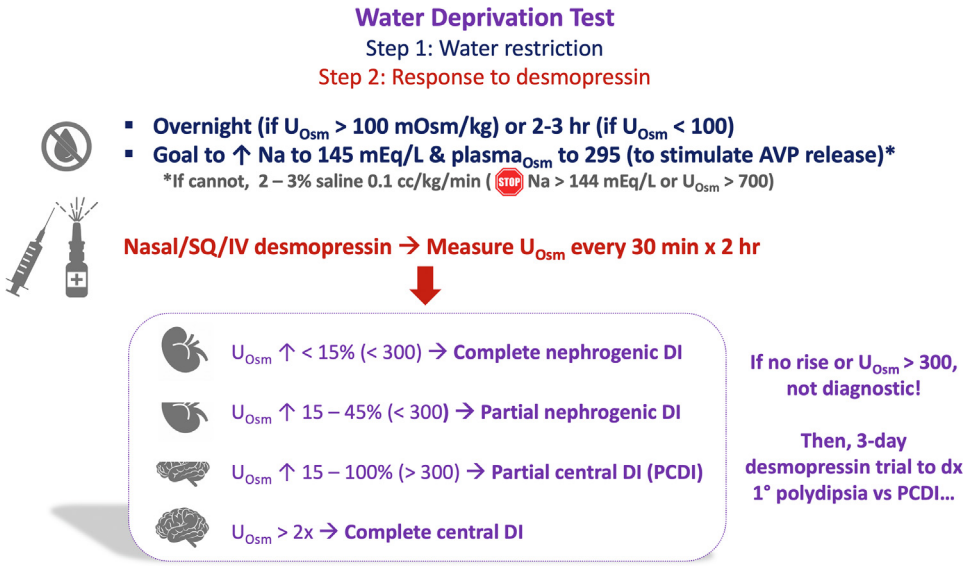

Figure 4. The water deprivation test can help diagnose diabetes insipidus, distinguish between a central and nephrogenic defect, and assess the severity of disease. Abbreviations: AVP, arginine vasopressin; DI, diabetes insipidus; IV, intravenous; SQ, subcutaneous; U_{Osm}, urinary osmolality. Used with permission from NephSIM (www.nephsim.com). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

by osmotic diuretics can be associated with an elevated UOsm, which is not a reflection of AVP activity and tubular water reabsorption but rather indicates the presence of an osmotic solute.[41] A higher luminal osmolality reduces the osmotic driving force for water reabsorption in the proximal tubule and in the medullary CD, thus increasing urinary free water loss. As glucose is osmotically active, severe hyperglycemia and sodium-glucose-linked transporter 2 inhibitors cause glycosuria and osmotic diuresis. This diuresis can ultimately cause hypernatremia if there is inadequate water replacement.[42] In fact, serum sodium increased after 4 weeks of treatment with empagliflozin among study participants with chronic hyponatremia in the setting of syndrome of inappropriate antidiuresis despite an increase in UOsm and likely increase in electrolyte-free water excretion.[43]

Azotemia in the recovery of both obstructive nephropathy and acute tubular necrosis may lead to an abundance of urinary urea excretion and, thus, excess kidney free water excretion as a result of osmotic diuresis. Urea raises the serum sodium concentration by inducing polyuria and, thus, increases net urinary free water excretion.[44] Partially due to this mechanism, urea is commercially available to treat hyponatremia.

Osmotic diuretics may be used for the treatment of hypervolemia or increased ICP. Mannitol is a polysaccharide diuretic that inhibits tubular reabsorption of water and electrolytes, leading to excess water losses and potentially causing hypernatremia.

HYPERNATREMIA FROM SODIUM GAIN

Excess sodium out of proportion to water can cause hypernatremia with volume expansion or edema.[45,46] Sodium can enter the body enterally or parenterally, and hypernatremia can be intentional, accidental, or iatrogenic. Sodium overload and toxicity from large, rapid ingestion or infusion of sodium has been noted in young infants related to formula use and adults of all ages (intentional or iatrogenic). In the hospital setting, excess sodium can be administered in hypertonic solutions (eg, 3% saline) to intentionally induce hypernatremia for the treatment of increased ICP. Inadvertent replacement of hypotonic volume losses with excess isotonic or hypertonic fluids may also occur. Although most patients with hypernatremia are hypovolemic, some patients may be hypervolemic due to the administration of intravenous hypertonic sodium chloride or sodium bicarbonate solutions. Hypernatremia in the hospital setting is commonly iatrogenic, especially in the critical care setting.[47,48] Patients who are both hypervolemic and hypernatremic may require both loop diuretics for volume overload along with free water replacement, as the loop diuretics will cause hypotonic fluid loss while also forcing natriuresis. Intravenous fluids, medication diluents, and nutrition (enteral and parenteral) should be evaluated and adjusted, with attention to sodium balance, volume status, and ongoing losses.

Outside the hospital, acute hypernatremia has been caused by massive soy sauce or salt consumption intended for use as an emetic, part of a spiritual ritual, or among near-drowning victims who have ingested sea water.[49-52] Plasma sodium levels rise within minutes and can continue to rise over the next few hours due to ongoing sodium absorption from the gastrointestinal tract. In these rare instances, acute hypernatremia can lead to significant neurological symptoms and even irreversible injury due to osmotic demyelination similar to overcorrection of hyponatremia due to a shift of intracellular fluid into the extracellular space.[53]

The initial treatment includes rapid free water replacement (ie, dextrose in water) which can be calculated with

the estimated water deficit, while attempting to account for the ongoing insensible losses. Dextrose concentrations should be minimized as possible to avoid iatrogenic hyperglycemia, even in those without diabetes mellitus. In those with excess sodium ingestion, nasogastric suction can remove residual stomach contents to prevent absorption of additional ingested sodium-containing fluids.[52] In rare circumstances, hemodialysis with lower sodium dialysate concentrations has been utilized to treat severe hypernatremia, especially when associated with acute kidney injury.[54] Severe acute hypernatremia from rapid salt ingestion that leads to rapid neurological damage may not improve despite prompt and aggressive hypotonic fluid administration.[50]

In the kidney, excess sodium reabsorption out of proportion to water reabsorption can occur with primary hyperaldosteronism or hypercortisolism, leading to a mild hypernatremia. Treatment of the underlying disorder with surgery and/or pharmacologic agents can restore normal homeostasis.

CONCLUSION

Sodium and water balance are tightly regulated through the stimulation of thirst, the secretion of AVP from the brain, and its activity in the kidney, to ensure that body osmolality is maintained in a narrow range. Extrarenal or renal hypotonic losses that are not replaced may lead to hypernatremia and may be the result of dysfunction of either AVP release or function. Treatment involves the replacement of lost water and management of the underlying disorder, when applicable.

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