REVIEW ARTICLE

The renal concentrating mechanism and the clinical consequences of its loss

Emmanuel I. Agaba, Mark Rohrscheib[1], Antonios H. Tzamaloukas[2]

Departments of Medicine, Division of Nephrology, Jos University Teaching Hospital, Jos, Plateau State, Nigeria, [1]University of New Mexico School of Medicine, Albuquerque, [2]Raymond G. Murphy Veterans Affairs Health Care System, Albuquerque, New Mexico, USA

ABSTRACT

The integrity of the renal concentrating mechanism is maintained by the anatomical and functional arrangements of the renal transport mechanisms for solute (sodium, potassium, urea, etc) and water and by the function of the regulatory hormone for renal concentration, vasopressin. The discovery of aquaporins (water channels) in the cell membranes of the renal tubular epithelial cells has elucidated the mechanisms of renal actions of vasopressin. Loss of the concentrating mechanism results in uncontrolled polyuria with low urine osmolality and, if the patient is unable to consume (appropriately) large volumes of water, hypernatremia with dire neurological consequences. Loss of concentrating mechanism can be the consequence of defective secretion of vasopressin from the posterior pituitary gland (congenital or acquired central diabetes insipidus) or poor response of the target organ to vasopressin (congenital or nephrogenic diabetes insipidus). The differentiation between the three major states producing polyuria with low urine osmolality (central diabetes insipidus, nephrogenic diabetes insipidus and primary polydipsia) is done by a standardized water deprivation test. Proper diagnosis is essential for the management, which differs between these three conditions.

Key words: Central diabetes insipidus, hypernatremia, hypertonicity, nephrogenic diabetes insipidus, urine concentration, vasopressin

Address for correspondence:
Emmanuel I. Agaba,
Nephrology Division, Jos University Teaching Hospital, PMB 2076, Jos, Jos-Nigeria.
E-mail: eiagaba@yahoo.com

INTRODUCTION

The regulation of external water balance, which is fundamental for maintenance of health and life, is achieved by integration of water intake and water loss. Water loss is physiologically regulated by the combined action of the posterior pituitary and the kidneys.[1] Abnormalities in water balance are clinically translated into abnormalities in tonicity that is in the osmotic property of the extracellular fluid (or serum) to make cells suspended in it swell through acquisition of fluid from the extracellular compartment (hypotonicity), shrink through loss of fluid to the extracellular compartment (hypertonicity) or maintain their volume (normal tonicity).

Abnormalities in tonicity produce clinical manifestations primarily through the neurological system. The laboratory surrogate values for hypotonicity are hyponatremia and low plasma osmolality while the surrogate values for hypertonicity are hypernatremia and, in the case of hyperglycemia, increased serum effective osmolality (2 × {serum sodium} + {serum glucose in mg/dL}/18).

This review is concerned with certain abnormalities in water balance that cause hypertonicity. The review is divided into three parts, a brief overview of the mechanism of water conservation by the human kidney and two conditions that cause hypertonicity through excessive water loss through the kidneys, central diabetes insipidus and nephrogenic diabetes insipidus. Hypertonic states that are not analyzed in this review include inadequate water intake, excessive water loss through the gastrointestinal track or skin, ingestion or infusion of hypertonic solutions, generation of excessive solute with extracellular distribution (such as in hyperglycemia) and excessive renal solute diuresis (osmotic diuresis). These conditions must be differentiated from the syndromes of diabetes insipidus in patients presenting with hypertonicity. The main characteristic of hypertonicity caused by either central or nephrogenic diabetes insipidus is the production of inappropriately dilute urine. This makes understanding of the principles of regulation of water excretion indispensable for physicians treating patients with diabetes insipidus.

Access this article online	
Quick Response Code:	Website: www.nigeriamedj.com
	DOI: 10.4103/0300-1652.104376

PHYSIOLOGY OF WATER EXCRETION

The mammalian kidneys are capable to dissociate the excretions of water and solute by varying urinary solute concentration (osmolality). Two features allow this dissociation of excretions: (a) The unique anatomic and functional characteristics of the nephron parts which are responsible for urinary dilution and concentration, and (b) the anatomic and functional integrity of the regulatory mechanism for urinary concentration (vasopressin release).

The anatomic arrangement of the renal medulla, the main site of urinary concentration and dilution, is orderly. Descending limbs of Henle are closely opposed to ascending limbs and to bundles of vasa recta, whereas the interstitium is highly organized.[2] The anatomic proximity of the structures with countercurrent flows of tubular fluid and blood, plus the solute and water permeabilities and transport characteristics of each nephron segment and vessel, allow fluid and solute exchanges between ascending and descending medullary structures. These exchanges are of paramount importance in the generation and maintenance of medullary interstitial hypertonicity and, therefore, in the elaboration of concentrated urine.[3] A study of osmolality in the different nephron parts reveals the anatomic location of the diluting and concentrating nephron segments.

OSMOLALITY OF TUBULAR FLUID

Absorption of fluid in the convoluted parts of the proximal tubule is approximately isotonic. Therefore, plasma and proximal tubular fluid osmolalities are almost equal. The tubular fluid becomes progressively more hyperosmolar as it descends through the straight segment of the proximal convoluted tubule and the descending limb of Henle towards the tip of Henle's loop. In these segments, tubular fluid hyperosmolality is created by two mechanisms: (a) Osmotic transfer of water from the tubular lumen into the hypertonic medullary interstitium, and (b) addition of solute, mainly sodium chloride and urea plus, to a smaller extent, potassium salts, from the interstitium into the tubular lumen.

After tubular fluid passes through the tip of Henle's loop, tubular fluid osmolality decreases progressively in the ascending parts of the loop. In contrast to water permeability in the thin descending limb of Henle, which is high, water permeability in the ascending segments of Henle's loop is exceedingly low regardless of plasma vasopressin level. Furthermore, the ascending segments of the limb of Henle have high permeabilities for the solutes making up the bulk of the osmotic concentration in the tubular fluid in these segments (chloride, sodium, urea), and possess, at least in the thick ascending limb of Henle, potent mechanisms of solute transfer, such as the apical NKCC2 channel (Na-K-2CI cotransporter). The progressive decrease in tubular fluid osmolality in these segments is, therefore, mediated through solute, mainly sodium chloride, transfer from the tubular lumen into the medullary interstitium.

As tubular fluid osmolality decreases progressively in the ascending limb of Henle, it reaches a point where it becomes equal to plasma osmolality. From that point on, further loss of intratubular solute results in the elaboration of a progressively more hypotonic tubular fluid. In physiologic states, the tubular fluid that issues out of the macula densa is always hypotonic to plasma. Loop diuretics poison the transport of chloride salts out of the thick ascending limb of Henle. The part of the ascending limb between the point where the tubular fluid becomes isotonic and the macula densa constitutes a part of the diluting segment of the kidney. The very low water permeabilities of the ascending parts of Henle's loop allow the creation of significant differences in osmolality between tubular fluid and surrounding medullary interstitium. At any transverse level through the outer renal medulla, interstitial fluid osmolality is substantially higher than the osmolality in the ascending limb of Henle.

In water diuresis, tubular fluid osmolality decreases further between macula densa and renal papilla. The mechanism of this part of the dilution of tubular fluid is also solute removal, as there is evidence supporting the view that water is transferred osmotically from the tubular lumen into the hypertonic interstitium even in water diuresis (water permeability of the collecting ducts is substantial even in the absence of vasopressin). Under antidiuretic conditions, however, water permeability of the collecting ducts, particularly of the inner medullary segment, is greatly increased under the influence of vasopressin.[4] Therefore water transfer out of the collecting ducts into the hypertonic interstitium is greatly facilitated, and the urine becomes hypertonic. The collecting ducts constitute the concentrating segment of the nephron.

OSMOLALITY IN RENAL MEDULLA

Under physiologic conditions, there is always an axial osmotic gradient in the renal medullary interstitium. Interstitial fluid osmolality, which is equal to plasma osmolality in the renal cortex, progressively increases in the renal medulla between the cortico-medullary junction and the tip of the renal papilla. Since urinary concentration is obtained by passive transfer of water from the tubular fluid into the hypertonic medulla, the generation and maintenance of the interstitial axial osmolality gradient in the renal medulla is an indispensable feature of the urinary concentration. The bulk of the solute responsible for the medullary interstitial hyperosmolality is made up by sodium chloride and, in the inner medulla, primarily by urea. The generation and maintenance of the axial osmolality gradient in the renal medulla requires

energy expenditure. The energy sources for this function are provided by the different sodium (and potassium) pumps present in the epithelial cells of the ascending limbs of Henle. The main energy source is the Na-K ATPase of the basolateral membranes of the tubular cells. The effect of the energy expenditure is amplified by the transfer of solutes and water between structures with countercurrent flows (ascending and descending tubules, blood vessels). The low medullary blood flow in comparison to the cortical blood flow prevents the rapid transfer of solutes entering the vasa recta by the countercurrent process away from the renal medulla and, therefore, the dissipation of the medullary hypertonicity. An informative analysis of the countercurrent mechanisms in the kidneys has been provided.[5]

Unlike the mathematical models of the countercurrent multiplication system, the quantitative description of urinary dilution and concentration is relatively simple. If U_{Na} and U_K are the urinary sodium and potassium concentration respectively and is V the urine volume, free water clearance (C_{H20} = the volume of water that would be needed to be added to an isotonic solution containing exactly the amount of solute present in the urine to produce the urine osmolality in a dilute urine) is:

$$C_{H2}=V\times(1-\{U_{Na}+U_K\}/P_{Na}) \quad (1)$$

If the urine is more concentrated than plasma, negative free water clearance (Tc_{H20} = the volume of water needed to be removed from an isotonic solution containing exactly the amount of solute present in the urine to produce the urine osmolality) is:

$$Tc_{H20}=V\times(\{U_{Na}+U_K\}/P_{Na}-1) \quad (2)$$

Another useful notation is the minimal and maximal urinary osmolality that can be achieved by normal kidneys. In humans, minimal osmolality is around 50 mOsm/kg, while maximal urinary osmolality may reach 1,200 mOsm/kg in protein replete, young healthy subjects. The water loading and water deprivation tests study the ability of individual patients with abnormalities in tonicity to maximally dilute or concentrate their urine when subjected to an appropriate challenge.

Vasopressin release and mode of action

Arginine vasopressin is the antidiuretic hormone (ADH) of humans. It is a 1,100 dalton nonapeptide synthesized as a much larger pro-hormone in the cell bodies of hypothalamic neurons located primarily in the supraoptic and paraventricular nuclei.[6] The pro-hormone travels down neuronal axons through the pituitary stalk into the posterior lobe of the pituitary gland, where it is stored as complexes with neurohypophysin II. When the neuron is stimulated, the complexes are secreted into the circulation by exocytosis, and they separate after discharge freeing vasopressin in the circulation.

Vasopressin is released under a variety of physiological and pathological stimuli

The discussion in this review will be limited to the two stimuli that have proven physiologic significance, namely hypertonicity (increased effective osmolality) and hypovolemia. Vasopressin is the regulatory hormone of body fluid osmolality and plays a major role in the defense against hypovolemia. Osmoreceptors sensing plasma tonicity are most probably located in the hypothalamus close to the supraoptic nuclei. In the physiologic range of plasma osmolality (280-290 mOsm/kg) and vasopressin concentration (0-5 pg/mL), a change in plasma osmolality equal to one percent results in a change in plasma vasopressin concentration equal to 1 pg/mL. The corresponding change in urine osmolality is 200-250 mOsm/kg.[7]

The afferent pathway for vasopressin release secondary to volume depletion starts with baroreceptors located in the aortic arch and the carotid sinus. At low levels of volume depletion, this mechanism of vasopressin release is insensitive. The rises in plasma vasopressin concentration resulting from extracellular volume losses less than 10% are minor or none. However, extracellular volume losses exceeding 15% produce large increases in plasma vasopressin levels regardless of plasma osmolality.[8]

Vasopressin receptors and water channels

Circulating vasopressin is bound to receptors found in many organs, including kidneys, liver, brain and vascular smooth muscle. Vasopressin receptors belong to a family of integral proteins containing 371 aminoacids, with seven membrane spanning sites. The amino-terminal is extracellular, while the carboxy-terminal is located intracellularly. These receptors are G-protein coupled receptors for vasopressin and related hormones (e.g., oxytocin).

The receptors for vasopressin that have been cloned include VIa (smooth muscle, liver), V1b (pituitary) and V2 (kidney). Stimulation of VIa and V1b receptors causes hydrolysis of phosphatidylinositol and intracellular calcium mobilization, while stimulation of V2 receptors causes intracellular release of cyclic AMP. Five sites with vasopressin receptors have been identified in the kidney (9): The glomerular mesangial cells (VIa receptors), the vasa recta (VIa receptors), the medullary interstitium (VIa receptors), the epithelial cells of the medullary thick ascending limb of Henle (V2 receptors), and the basolateral (antiluminal) membranes of the principal cells of the collecting ducts (V2 receptors). The intercalated cells of the collecting ducts have no AVP receptors. In several of these sites, such as the mesangia1 cells, vasopressin has trophic and functional effects.

In contractile cells (mesangium, vasa recta), vasopressin-induced increases in intracellular calcium

concentration result in myosin phosphorylation and contraction of the cells. Contraction of vasa recta reduces the dissipation of medullary interstitial solute and assists in the maintenance of medullary hypertonicity. In mesangial cells and medullary interstitial cells, the vasopressin-induced intracellular release of calcium stimulates synthesis of prostaglandin E, which modulates vasopressin-induced water absorption.[9]

In the medullary thick ascending limb of Henle, vasopressin-induced increase in cyclic AMP results in increased reabsorption of chloride salts. In this segment, cyclic AMP increases the number of potassium channels and Na-K-2Cl cotransporter units in the apical membrane, thus contributing to the increased reabsorption of chloride salts.[10] Increased transfer of chloride salts outside the lumen of the medullary thick ascending limb of Henle increases medullary hypertonicity. However, the site of the major action of vasopressin on urinary osmolality is the collecting duct. The cloning of the V2 receptor and the discovery of the water channels (aquaporins) in the membranes of the water permeable cells produced a quantum leap in our understanding of water handling by the renal tubules.

The gene for the V2 receptor is located in the X–chromosome and mutations in this receptor are the causes of the most common (the sex-linked) form of congenital nephrogenic diabetes insipidus.[11] The discovery of a 28 kd, 271 aminoacid integral protein spanning the wall of red cells in six sites, with intracellular location of both the amino- and the carboxy-terminal and the critical experiment establishing this compound as a water channel plus the demonstration of the mechanism by which this channel allows water transfers[12,13] made Dr Peter Agre a Nobel prize winner in 2003.

The original aquaporin (AQP1) is found in the cell membranes of erythrocytes, brain cells, endothelial cells, lung cells and other tissues. In the kidney, both the apical (luminal) and the basolateral (anti luminal) membranes of the epithelial cells of the proximal convoluted tubule and the descending limb of Henle have AQP1 in abundance.

This abundance of AQPl, which is constitutive and is not regulated by AVP, is the cause of the high water permeability of these segments. Mutation of the AQP1 gene is associated with a mild form of congenital nephrogenic diabetes insipidus.[14]

Of interest to the renal concentrating mechanism and its clinical disorders are the renal aquaporins AQP2, AQP3 and AQP4, which are located in the principal cells of the collecting ducts. AQP3 and AQP4 are located in the basolateral membrane. Under conditions of water diuresis (low plasma AVP levels), AQP2 is located primarily in the cytoplasm and only a small fraction of the total AQP2 molecules is inserted in the apical membrane. In antidiuresis (high plasma AVP levels), AQP2 is located in the apical membrane. AVP, therefore, controls the number of AQP sites in the apical membrane of the principal cells of the collecting duct. AVP binds to the V2 receptor in the basolateral membrane activating the V2 receptor/G-protein complex, which in its term activates adenylate cyclace leading to increased cyclic AMP production. The result is phosphorylation of cytoplasmic AQP2 and insertion of the phosphorylated in the apical membrane. Prostaglandin E2 inhibits AVP-induced increased water permeability of the collecting ducts by reducing cyclic AMP levels.

The increase in the permeability of the apical membrane to water under the influence of AVP is the result of the increased number of phosphorylated AQP2 in this membrane. Water entering the principal cells through the AQP2 sites exits the cells through the basolateral AQP3 and AQP4 channels. The onset of action of vasopressin on water permeability of the collecting duct is rapid, within seconds of its addition.[15]

Abnormalities in urinary concentration-the water deprivation test

Urinary concentrating ability is diminished by conditions affecting either vasopressin release (central or pituitary diabetes insipidus), or renal response to vasopressin (nephrogenic diabetes insipidus). The cardinal clinical manifestations of both syndromes are polyuria with dilute urine and hypertonicity. Primary polydipsia is another clinical state presenting with polyuria and dilute urine. The water deprivation test[16] is currently the method of choice for the differentiation between the three polyuric states presenting with large volumes of dilute urine.

The water deprivation test is performed by withholding water after the patient is well hydrated and by frequent (hourly) measurements of body weight and urine and serum osmolality. The test is completed when the patient loses 3% of body weight (5% of body water), which should produce a maximal physiologic response in vasopressin release. The test, which requires 10-12 hours for its completion in normal subjects, can take a much shorter time for patients with abnormalities in urinary concentration. It requires constant monitoring of the patients, because dehydration can become severe in patients unable to conserve water. The important findings at the end of this first phase of the test consist of a 5% increase in serum osmolality to ensure maximal physiologic stimulation of vasopressin release, measurement of urine osmolality to assess the effect of dehydration on the urinary concentrating mechanism, and a plasma vasopressin level. The test can be interpreted even when vasopressin measurements are not available, by administering exogenous vasopressin after the end of the first phase and recording the ensuing changes in urine osmolality. Table 1 shows the differentiation of the polyuric states with dilute urine by the water deprivation test and administration of exogenous vasopressin. Vasopressin

release as a result of water deprivation does not differ between patients with nephrogenic diabetes insipidus and normal subjects.

Central diabetes insipidus

Table 2 shows the etiology of Central diabetes insipidus (Central Dl).[17] In half or more than half of the cases with central DI, no cause can be ascertained (idiopathic). Head trauma, brain surgery and tumors, primary or metastatic, account for the majority of the cases with known etiology.

After brain surgery, urinary concentration and dilution abnormalities often follow a triphasic course, with an early phase of DI from destruction of the neurohypophysis followed in a few days by a phase of inappropriate ADH secretion due to the release of stored vasopressin. After another few days during which vasopressin stores are depleted, permanent DI is established. Breast carcinoma is the most common metastatic tumor causing central DI.[18] In the congenital form of the syndrome, which is inherited as an autosomal dominant or a sex-linked recessive condition, a selective depletion of neurosecretory granules appears to develop in the supraoptic and paraventricular nuclei.[19] The autosomal dominant variety is caused by mutations in the gene coding the vasopressin-neurohypophysin precursor. There is also an X-linked variant.

Clinically, complete central DI manifests with polyuria, up to 10 liters or more of dilute urine daily, and severe thirst. Polyuria and thirst persist unabated at night. Plasma osmolality and sodium concentration tend to be on the high side of the normal range in ambulatory patients with free access to water. If patients become bed-ridden, confused, or unable to consume water freely for whatever reason, severe hypernatremia with neurological manifestations (coma, seizures) can develop rapidly. For this reason, comatose patients, particularly after head trauma or brain surgery, require monitoring of urine volume, urine osmolality and plasma osmolality and sodium concentration. In some instances, prolonged polyuria of the magnitude of 10 liters daily leads to bladder dilatation, hydroureters and hydronephrosis.

The management of central DI includes management of water intake and drugs. Some patients with a partial defect in vasopressin secretion and intact thirst mechanism can be managed by increased intake of water only. Water intake is divided between day and night to avoid nocturnal dehydration. Other patients with partial central diabetes insipidus can be managed by drugs which either stimulate vasopressin release or enhance its action on the collecting ducts. Chlorpropamide in a dose of 250 mg once or twice a day,[20] or clofibrate in a dose of 500 mg four times a day,[21] or a combination of the two drugs, have been tried. Persistent hypoglycemia has led to failure of chlorpropamide treatment in several instances.

Table 1: The water deprivation test

Clinical state	Water deprivation test POsm* UOsm*	Endogenous ADH plasma level*	Exogenous ADH effect on Uosm
Normal	>3% rise >800	High	None
Central DI			
Complete	>3% rise <200	Absent	Increase >30%
Partial	>3% rise 300-700	Low	Increase >10%
Nephrogenic DI			
Congenital	>3% rise <300	High	None
Acquired	>3% rise 300-500	High	None
Primary (Psychogenic)			
Polydipsia	>3% rise >600	High	Increase <10%

ADH - Antidiuretic hormone; POsm: Plasma osmolality (mOsm/kg); UOsm: Urine osmolality (mOsm/kg); DI: Diabetes insipidus; * at end of water deprivation period, prior to exogenous vasopressin administration

Table 2: Causes of central diabetes insipidus

Congenital
Autosomal recessive
Sex-linked
Idiopathic (more than 50% of all cases)
Other causes
Brain tumors (benign, malignant)
Metastatic brain tumors (breast)
Meningioma
Head trauma, surgery
Brain thrombosis, haemorrhage, anaeurysms
Infections (meningitis, encephalitis, Guillain-Barre syndrome)
Granulomatous disease (tuberculosis, sarcoidosis, histiocytosis)
Pregnancy (increased vasopressinase activity, Sheehan's syndrome)

Several preparations of vasopressin are available for the treatment of central DI. Aqueous vasopressin is injected subcutaneously in a dose of 2-4 units every six hours. This preparation, which has a very short half-life (minutes) is used for comatose patients. Desmopressin acetate (DDAVP), which is a synthetic analogue of vasopressin with longer half-life and with a smaller effect on blood pressure than vasopressin, is currently the drug of choice. This medication comes in three preparations. The intravenous preparation of DDAVP for acute treatment, in a usual dose of 10 micrograms, is administered every 12 hrs. The tablet form of DDAVP for chronic states are administered in a dose of 0.2 micrograms every 12 to 24 hrs. Aerosol DDAVP is administered for chronic use by nasal spray in a dose of 2.5 to 20 micrograms every 12 to 24 hrs. Headache is the most common side effect of nasal desmopressin. Vasopressin tannate in oil, which has the longest half-life, is administered by deep subcutaneous or intramuscular injection in a dose of 2.5 units every 24 to 72 hrs. Sterile abscesses of the injection sites have been reported in some patients receiving this preparation. Once vasopressin is started patients should be cautioned to reduce fluid intake. Life-threatening hyponatremia with convulsions can develop rapidly if large water intake continues while the kidney is obligated to elaborate concentrated urine.

Nephrogenic diabetes insipidus (nephrogenic DI)

Nephrogenic DI is caused, in general, by two mechanisms

Loss of medullary hypertonicity because of anatomic disease of the kidney or functional disturbances, and inability of the collecting duct epithelium to respond to vasopressin. Table 3 shows the causes of nephrogenic DI. The most common form of congenital nephrogenic DI is inherited by an x-linked recessive pattern. V2 receptors are mutated in this syndrome, in which urinary excretion of cyclic AMP does not increase after vasopressin infusion, as it does in normal subjects. Affected males manifest the condition from birth with dehydration, hypertonicity, seizures, and, if the condition is not diagnosed on time, develop failure to thrive and mental retardation.[22] Hydronephrosis, enuresis and urinary infections are also encountered frequently.[23] Female carriers demonstrate inability to adequately concentrate the urine under conditions of water deprivation, but are usually asymptomatic.

More rare forms of nephrogenic DI, inherited as autosomal recessive or autosomal dominant, are caused by mutations in the AQP2 gene, which is located in chromosome 12. Patients with these forms of nephrogenic DI respond usually to vasopressin infusion by increasing the urinary excretion of cyclic AMP, but do not concentrate the urine. The management of the condition includes adequate water administration throughout the 24 hrs plus thiazide diuretics which block urinary dilution.

Acquired forms of nephrogenic DI are partial. The kidneys can respond to vasopressin by raising urinary osmolality to 300-500 mOsm/kg. Polyuria, therefore, is modest (3-5 liters per day) in these syndromes, and severe dehydration with hypertonicity is unlikely, except in comatose patients. AQP2 expression is decreased in chronic forms of acquired nephrogenic DI.[15] Among the drugs listed in Table 3 as causes of nephrogenic DI, lithium and demeclocycline, have great clinical importance. Lithium is used extensively in the management of the manic phase of the bipolar psychiatric illness. It produces polyuria routinely, and patients or their guardians should be warned about this side effect and the need for increased water intake during treatment. Lithium blocks adenylate cyclase and obliterates AQP2 expression.[15] Demeclocycline, which also inhibits adenylate cyclase and a site distal to cyclic AMP formation, is useful in the management of the inappropriate ADH secretion syndrome. Vasopressin receptor inhibitors are the newest agents in the management of inappropriate ADH secretion syndrome and other hyponatremias,[24] but are expensive. Although some reduction in medullary hypertonicity is present in both hypokalemia[25] and hypercalcemia,[26,27] it appears that the main mechanism of nephrogenic diabetes insipidus in both these conditions is a decreased response of the renal collecting ducts to vasopressin.

Table 3: Causes of nephrogenic diabetes insipidus

Absent or decreased collecting duct response to vasopressin
Congenital nephrogenic diabetes insipidus
Sex-linked
Autosomal recessive
Autosomal dominant
Drugs
Lithium, demeclocycline, amphotericin B, methoxyflurane
Hypokalemia
Hypercalcemia
Loss of medullary hypertonicity
Diseases affecting the renal medulla
Pyelonephritis, papillary necrosis, analgesic nephropathy, medullary cystic disease, polycystic kidneys, sjoegren's syndrome, amyloidosis, sarcoidosis, multiple myeloma
Drugs
Loop diuretics
Starvation
Low protein intake
Postrenal transplantation
Mixed pathogenesis (unresponsiveness to vasopressin plus loss of medullary hypertonicity)
Chronic renal failure
Postobstructive diuresis
Sickle cell disease

Renal diseases which disrupt the anatomic integrity and function of the renal medulla, or lead to relative increases in the medullary blood flow, lead to partial forms of nephrogenic diabetes insipidus, while diluting ability of the kidneys is, in general, preserved.[28] Table 3 lists important renal conditions associated with nephrogenic DI. Loop diuretics decrease medullary hypertonicity by inhibiting its energy source (chloride pumps). Starvation leads to urea depletion and to low glomerular filtration rate with consequent low rate of chloride salt absorption at the ascending limb of Henle.[29] In the first few days after renal transplantation and after correction of a urinary obstruction, urinary concentrating ability is impaired because of large osmotic diuresis.[30]

The inability to concentrate the urine in advanced renal insufficiency is due, at least in part, to disruption of the anatomy of the renal medulla and to increased solute load (osmotic diuresis) per functioning nephron.[31] However, there is evidence that the epithelium of the collecting ducts from experimental animals with chronic renal failure does not respond appropriately to vasopressin.[32] Post-obstructive diuresis is due to osmotic diuresis, to a large extent.[33] However, decreased medullary hypertonicity,[34] increased medullary blood flow,[35] and decreased epithelial response to vasopressin, probably mediated by increased production of prostaglandin E2,[36] contribute to the decrease in renal concentrating ability in this syndrome. Finally, in sickle cell disease or trait, destruction of the medullary anatomic structure is the most probable cause of nephrogenic DI.[37] However, the concentrating defect is reversible, at least in the early stages.[38] It appears, therefore, that other factors,

such as increased renal medullary blood flow, and, possibly, changes in the responses of the epithelium of the collecting ducts to vasopressin may contribute to the concentrating defect that is present in subjects with sick1e cell disease or trait.

The management of nephrogenic DI is symptomatic. Large amounts of water and salt, divided throughout the 24 hours, should be administered to prevent dehydration. For most of the clinical states discussed, including chronic renal failure and post-obstructive diuresis, diluting ability is maintained while concentrating ability is severely impaired. In these instances, inhibiting the diluting mechanism with thiazide diuretics can be helpful. If the underlying condition (drugs, multiple myeloma, sarcoidosis, etc) is treatable, treatment of the condition may ameliorate or reverse the renal concentrating defect.

REFERENCES

1. Andreoli TE. Water: Normal balance, hyponatremia and hyponatremia. Ren Fail 2000;22:711-35.
2. Bulger RE, Nagle RB. Ultrastructure of the interstitium in the rabbit kidney. Am J Anat 1973;36:183-203.
3. Kriz W. Structural organization of the renal medulla: Comparative and functional aspects. Am J Physiol 1981; 241:R3-16.
4. Imai M, Taniguchi J, Yoshitomi K. Transition of permeability properties along the descending limb of long-looped nephron. Am J Physiol 1988;254:F323-8.
5. Knepper MA, Gamba G. Urinary concentration and dilution. In Brenner and Rector's The Kidney. In: Brenner BM, editor. 7th ed. Philadelphia: Saunders; 2004. p. 599-636.
6. Zimmerman EA, Robinson AG. Hypothalamic neurons secreting vasopressin and neurohypophysin. Kidney Int 1976;1:12-24.
7. Robertson GL, Shelton RL, Athar S. The osmoregulation of vasopressin. Kidney Int 1976;10:25-37.
8. Dunn FL, Brennan TJ, Nelson AE, Robertson GL. The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 1973;52:3212-9.
9. Margolis B, Angel J, Kremer S, Skorecki K. Vasopressin action in the kidney. Overview and glomerular actions. In Vasopressin. In: Cowley AV, Liard JF, Ausiello DA, editors. New York: Raven Press; 1988. p. 197.
10. Hebert SC, Reeves WB, Molony DA, Andreoli TE. The medullary thick limb: Function and modulation of the single-effect multiplier. Kidney Int 1987;31:580-9.
11. Bichet DG. Hereditary nephrogenic diabetes insipidus. Adv Nephrol Necker Hosp 1991;20:175-89.
12. Agre P. Homer-Smith award lecture. Aquaporin water channels in kidney. J Am Soc Nephrol 2000;11:764-77.
13. Preston GM, Carroll TP, Guggino WP, Agre P. Appearance of water channels in Xenopus oocytes expressing red cell CHIP28 protein. Science 1992;25:385-7.
14. King LS, Choi M, Fernandez PC, Cartron JP, Agre P. Defective urinary concentrating ability due to a complete deficiency of aquaporin-1. N Engl J Med 2001;345:175-9.
15. Nielsen S, Kwon TH, Christensen BM, Promeneur D, Froklaer J, Maples D. Physiology and pathophysiology of aquaporins. J Am Soc Nephrol 1999;10:647-63.
16. Miller M, Dalakos T, Moses AM, Fellerlman H, Streeten DH. Recognition of partial defects in antidiuretic hormone secretion. Ann Int Med 1970;13:721-9.
17. Moses AM, Norman DD. Diabetes insipidus and the syndrome of inappropriate antidiuretic hormone secretion. Adv Intern Med 1980;27:73-100.
18. Yap HY, Tashima CK, Blumenschein GR, Eckles N. Diabetes insipidus and breast cancer. Arch Intern Med 1979;139:1009-112.
19. Braverman LE, Mancini JP, McGoldrick DM. Hereditary diabetes insipidus. Acase report with autopsy findings. Ann Int Med 1965;63:503-6.
20. Moses AM, Numann P, Miller M. Mechanism of chlorpropamide-induced antidiuresis in man: Evidence for release of ADH and enhancement of peripheral action. Metabolism 1973;22:59-66.
21. Moses AM, Howantiz J, Van Gement M, Miller M. Clofibrate-induced antidiuresis. J Clin Invest 1973;52: 535-42.
22. Orloff J, Burg MB. Vasopressin-resistant diabetes insipidus. In the Metabolic Basis of Inherited Disease. In: Stanbury J, Wyngaarden JB, Frederickson NS, editors. 3rd ed. New York: McGraw-Hill; 1972. p. 1567.
23. Van Lieburg AF, Knoers AM, Monnens LA. Clinical presentation and follow-up of 31 patients with congenital nephrogenic diabetes insipidus. J Am Soc Nephrol 1999;10:1956-64.
24. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007; expert panel recommendations. Am J Med 2007;120:S1-21.
25. Cox N, Singer I. Lithium and water metabolism. Am J Med 1975;59:153-7.
26. Beck N, Webster SK. Impaired urinary concentrating ability and cyclic AMP in K-depleted rat kidney. Am J Physiol 1975;231:1204-8.
27. Beck N, Singh H, Reed SW, Murdaugh HV, Davis BB. Pathogenic role of cyclic AMP in the impairment of urinary concentrating ability in acute hypercalcemia. J Clin Invest 1974;54:1049-54.
28. Berl T, Anderson RJ, McDonald KM, Schrier RW. Clinical disorders of water metabolism. Kidney Int 1976;10:117-32.
29. Rector BC, Jr. Renal concentrating mechanism. In Disturbances in Body Fluid Osmolality. In: Andreoli TE, Grantham JJ, Rector FC Jr, editors. Bethesda: American Physiological Society; 1977. p. 179.
30. Henderson LW, Nolph KD, Puschett JB, Goldberg M. Proximal tubu1ar malfunction as a mechanism of diuresis after renal homotransplantation. N Engl J Med 1968;278:467-73.
31. Tannen RL, Regal EM, Dunn MJ. Schrier RW. Vasopressin-resistant hyposthenuria in advanced chronic renal disease. N Eng J Med 1969;280:1135-41.
32. Fine LG, Schlondorff D, Trizna W, Gilbert RM, Bricker NS. Functional profile of the isolated uremic nephron. Impaired water permeability and adenylate cyclase responsiveness of the cortical collecting tubule to vasopressin. J Clin Invest1978;61:1519-27.
33. Witte MR, Short FA, Hollander W, Jr. Massive polyuria and natriuresis following relief of urinary tract obstruction. Am J Med 1970;37:320-6.
34. Honda N, Aizawa C, Morikawa A, Yoshitori Y. Effect of ureteral pressure elevation on renal medullary osmolal concentrations in hydropenic rabbits. Am J Physiol1971;220:698-703.
35. Selkurt EE. Effects of ureteral blockade on renal blood flow and urinary concentrating ability. Am J Physiol 1971;221:698-703.
36. Anderson RJ, Berl T, McDonald D, Schrier RW. Evidence of an *in vivo* antagonism between vasopressin and prostaglandin in the mammalian kidney. J Clin Invest 1975;56:420-6.
37. Statius van Eps LW, Pinedo-Veels C, De Vries GH, de Konig J. Nature of concentrating defect in sickle-cell nephropathy. Lancet 1970;1:450-2.
38. Keitel HG, Thompson D, Itano HA. Hyposthenuria in sickle-cell anemia: A reversible renal defect. J Clin Invest 1956;35:998-1007.

How to cite this article: Agaba EI, Rohrscheib M, Tzamaloukas AH. The renal concentrating mechanism and the clinical consequences of its loss. Niger Med J 2012;53:109-15.

Source of Support: Nil, **Conflict of Interest:** None declared.