

Chapter 2

Physiology of Water Balance and Pathophysiology of Hyponatremia

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Introduction

The normal function and ultimate survival of every cell in the human body depends on its presence within the proper milieu. The tonicity of the extracellular fluid is a key component of that environment and acts as an important determinant of the intracellular composition as well. Myocyte function, signaling pathways, cell membrane integrity, and neuronal depolarization are just a few examples of crucial aspects of our physiology that depend on the constancy of the ambient osmolarity. As the single most important determinant of extracellular tonicity, the concentration of sodium in the serum must be tightly regulated for these myriad cellular processes to be discharged normally. Correspondingly, significant deviations in the serum sodium concentration are tolerated poorly and result in cellular dysfunction. The stability of the serum sodium concentration within a narrow range despite wide variations in water intake, solute ingestion, and non-urinary water losses is the result of a strict balance between water intake and water output. This balance is achieved primarily through regulation of urinary tonicity. When these balance mechanisms are disrupted or overwhelmed, dysnatremias ensue.

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Physiology of Water Balance

Concept of Water Balance and Its Relationship to Serum Sodium Concentration

Central to the understanding of the serum sodium concentration and its regulation is the concept of *effective osmolarity*. An effective osmole is a species in the aqueous phase of the plasma that does not readily penetrate cell membranes and therefore acts to hold water within the extracellular space. By this description, a membrane-impermeable molecule like glucose is an effective osmole while a molecule with free membrane permeability such as urea would be considered an ineffective osmole. (It must be noted that while there is some delay in equilibration of urea across various compartments, it is a highly permeable molecule and in steady state should be considered an ineffective solute.). While a variety of species contribute to the overall effective plasma osmolarity, sodium is by far the most important. In fact, sodium salts account for more than 95 % of the effective osmoles under normal circumstances, and the effective plasma osmolarity (P_{osm}) can therefore be estimated with the following simple equation:

$$\text{Effective } P_{\text{osm}} \cong 2 \times \text{Plasma sodium concentration.} \quad (2.1)$$

This relationship means that the plasma sodium concentration accurately reflects the plasma osmolarity in the vast majority of clinical situations, and therefore, overall body osmoregulation relies primarily upon the regulation of plasma sodium concentration.

As a result, further understanding of disorders of osmolarity relies on a clear understanding of the definition of the sodium concentration. In that regard, expansion of the plasma osmolarity definition is helpful. Because of the osmotic equilibrium between the intracellular and extracellular compartments, the effective P_{osm} is equal to the effective osmolarity throughout the entire total body water, regardless of compartment:

$$\text{Effective } P_{\text{osm}} = \text{Effective osmolarity of the total body water.} \quad (2.2)$$

The effective osmolarity of the total body water is the ratio between the total body's effective solutes and the total body water, so therefore:

$$\text{Effective } P_{\text{osm}} = \frac{\text{Effective extracellular solutes} + \text{Effective intracellular solute}}{\text{Total body water}}. \quad (2.3)$$

Because the chief effective extracellular solute is exchangeable sodium and the chief effective intracellular solute is exchangeable potassium (where

“exchangeable” refers to the store of ions unbound and free for exchange between compartments), Eq. (2.3) can be reapproximated in the following way:

$$\text{Effective } P_{\text{osm}} = \frac{(2 \times \text{exchangeable sodium}) + (2 \times \text{exchangeable potassium})}{\text{Total body water}}, \quad (2.4)$$

where the 2 multiplier accounts for the accompanying anions. Substituting (2.1) into (2.4) yields the following [1]:

$$\text{Plasma sodium concentration} \cong \frac{\text{Exchangeable sodium} + \text{Exchangeable potassium}}{\text{Total body water}}. \quad (2.5)$$

Considering these determinants of the plasma sodium concentration allows for a conceptual framework for understanding disorders of sodium concentration. The total body sodium is regulated by mechanisms designed to preserve intravascular volume, blood pressure, and tissue perfusion; these regulatory mechanisms do *not* target any specific osmolarity or sodium concentration. Instead, the maintenance of a stable serum sodium concentration is accomplished chiefly through regulation of total body water, the denominator of (2.5). A variety of mechanisms act through the kidney to regulate total body water content so that changes in total body water match changes in exchangeable sodium and potassium, thereby producing a stable serum sodium concentration despite any possible variations in the absolute amounts of solute present.

Given the importance of total body water regulation, the balance between water intake and excretion must be strictly maintained. As such, this concept of water balance is absolutely essential to an understanding of hyponatremia (as well as hypernatremia). As described in detail below, the regulation of water intake is accomplished largely through control of thirst, while water excretion is regulated chiefly through urinary dilution and concentration as warranted by the demands of the clinical setting. It follows that abnormalities in water balance are responsible for the dysnatremias, and with respect to hyponatremia, this fundamental concept means that *all cases of hypotonic hyponatremia reflect either absolute or relative positive water balance*. Put another way, hyponatremia supervenes when the intake of water exceeds the kidney’s ability to excrete sufficiently dilute urine. Relative water retention most often arises when urinary diluting mechanisms are disturbed, but it can also occur when urinary dilution is intact.

A full understanding of the pathogenesis of hyponatremia in light of water balance considerations requires attention to both sides of the water balance equation. On the output side, the body loses roughly 1,100 mL of water per day from stool (200 mL) and from evaporation at skin (500 mL) and respiratory tract surfaces (400 mL) [1]. In addition, there is a minimum amount of water that the kidney must excrete as part of the process of solute clearance. To maintain electrolyte balance, an individual ingesting a typical North American diet must excrete a total of

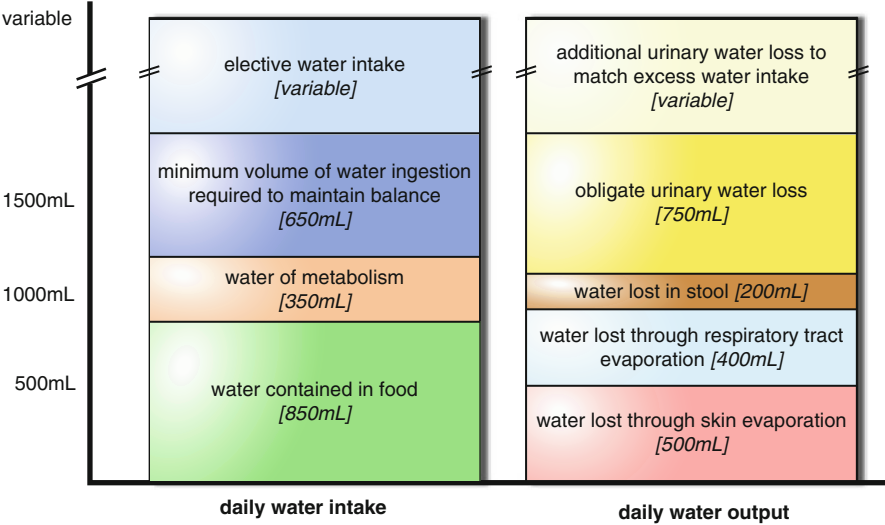


Fig. 2.1 Cumulative daily water balance. The values shown above assume normal skin, respiratory tract, and stool losses (i.e., an absence of excessive sweating, tachypnea, mechanical ventilation, and diarrhea). In addition, the volume of obligate urinary water loss is based on calculations of an 80-kg subject consuming a standard North American diet who has normal urinary concentrating ability, as described in the text

400 mOsm of consumed electrolytes (comprised primarily of sodium, potassium, and their accompanying anions). Additionally, roughly 500 mOsm of urea must be excreted each day—100 mOsm produced by normal catabolism plus 400 mOsm from dietary protein metabolism (every gram of ingested protein yields 5 mOsm of urea, an 80 kg person consuming 1 g protein per kilogram of body weight produces $80\text{ g} \times 5\text{ mOsm} = 400\text{ mOsm}$ of urea). With a maximum urinary concentration of 1,200 mOsm/L, these 900 mOsm of solute can be excreted in a minimum of 750 mL of water. Therefore, in total, a minimum of 1,850 mL of water is lost per day by the average size person on a North American diet (Fig. 2.1).

On the intake side, there are three principal components to consider—water ingested in liquids, water consumed in solid foods, and water produced by metabolism. Water input from ingested food and metabolism is relatively fixed at about 1,200 mL per day, closely matching the fixed non-urinary losses [1] (Fig. 2.1). Therefore, to stay in balance and match the minimum output of 1,850 mL, a minimum of 650 mL of water must be ingested each day, which roughly matches the obligate urinary water losses. When that precise amount of fluid is ingested, water balance is easily maintained. However, the kidney has evolved a remarkable ability to vary the tonicity of urine so that balance is maintained in the setting of wide variations of intake and non-renal water losses. When any amount of fluid in excess of the 650 mL is ingested (which is common due to normal drinking habits dictated by social norms), the additional free water is excreted through dilution of the urine. Conversely, when an individual drinking the average 2 L of fluid per day

develops increased water losses above normal (from diarrhea, sweating, increased respiratory losses, etc.), balance is maintained through concentration of the urine as well as the stimulation of thirst in order to increase fluid intake. Any significant disturbances in these processes of matching water intake to output will result in dysnatremias. Because urinary tonicity regulation is key in the maintenance of water balance, a more precise and quantitative understanding of urinary free water clearance is warranted.

A Quantitative Approach to Water Clearance

Conceptually, it can be useful to consider any given volume of urine as comprised of two separate components. First, all solutes cleared by the kidney can be thought of as being excreted in a urinary component whose concentration is isotonic to the plasma. This isotonic solute clearance (C_{osm}) is excreted in combination with a second urinary component, the clearance of water (C_{water}). These two clearances comprise the total urine volume flow (V), such that

$$V = C_{\text{osm}} + C_{\text{water}}. \quad (2.6)$$

The first component, C_{osm} , can be viewed as a nonregulated quantity, determined exclusively by the clearance demands created by the individual's solute intake. Water clearance, on the other hand, is highly regulated in order to achieve the necessary water balance, primarily through the actions of the pituitary hormone arginine vasopressin (AVP).

Since water balance is crucial to regulation of plasma osmolarity, further exploration of the C_{water} term is essential for understanding disorders of plasma osmolarity. The clearance of any substance is equal to the product of urine flow and the ratio of its urinary concentration to its plasma concentration:

$$C_x = V \times \left(\frac{U_x}{P_x} \right). \quad (2.7)$$

Substituting this definition for C_{osm} into the urine flow equation (2.6) yields the following:

$$V = \left[V \times \left(\frac{U_{\text{osm}}}{P_{\text{osm}}} \right) \right] + C_{\text{water}}, \quad (2.8)$$

where U_{osm} is the urine osmolarity and P_{osm} is the plasma osmolarity. This relationship can be further rearranged to the following:

$$C_{\text{water}} = V \times \left(1 - \frac{U_{\text{osm}}}{P_{\text{osm}}} \right). \quad (2.9)$$

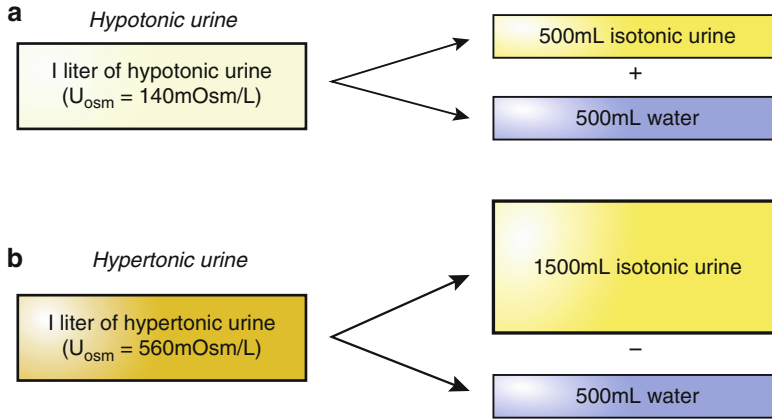


Fig. 2.2 Positive and negative water clearance. Panel (a) shows 1 L of hypotonic urine ($U_{\text{osm}} = 140 \text{ mOsm/L}$) conceptualized as the sum of 500 mL of isotonic urine and 500 mL of water. This is an example of positive water clearance, in which free water is lost from the body. Panel (b) shows 1 L of hypertonic urine ($U_{\text{osm}} = 560 \text{ mOsm/L}$) conceptualized as 1,500 mL of isotonic urine with 500 mL of water removed. This is an example of negative water clearance, in which free water is retained through absorption. Both panels assume a plasma osmolarity of 280 mOsm/L

From this equation, it is evident that when U_{osm} is less than P_{osm} , the urine is hypotonic and free water excretion is positive. Conversely, when U_{osm} exceeds P_{osm} , the urine is concentrated above plasma, and free water excretion is negative.

To illustrate this concept, consider a situation in which the urine is hypotonic compared to the plasma (i.e., $U_{\text{osm}} < P_{\text{osm}}$). If a patient with a plasma osmolarity of 280 mOsm/L excretes a liter of urine with an osmolarity of 140 mOsm/L, then the free water clearance using (2.9) above would be +500 mL ($C_{\text{water}} = 1 \text{ L} \times (1 - (140 \text{ mOsm/L}/280 \text{ mOsm/L})) = 0.5 \text{ L}$). This liter of urine can therefore be conceptualized as 500 mL of isotonic urine and 500 mL of water. The positivity of the free water clearance value indicates that this excretion of urine has produced a net loss of water from the body.

Conversely, if the same patient excretes a liter of hypertonic urine with an osmolarity of 560 mOsm/L, then the free water clearance would be -500 mL ($C_{\text{water}} = 1 \text{ L} \times (1 - (560 \text{ mOsm/L}/280 \text{ mOsm/L})) = -0.5 \text{ L}$). Conceptually, this liter of urine can be viewed as 1.5 L of isotonic saline with 500 mL of water removed. This negative water clearance corresponds to water reabsorption in the kidney, producing hypertonic urine and the net retention of water. Figure 2.2 illustrates these concepts.

It is important to recognize that both of the osmolarity terms in (2.9) include the contribution of urea, but because urea is an ineffective osmole due to its cell membrane permeability. A more clinically useful tool that excludes urea is the electrolyte free water clearance, which better predicts directional changes in serum sodium concentration. This term, the *electrolyte-free water clearance* ($C_{\text{water}}^{\text{e}}$), is defined by the following equation: [2]

$$C_{\text{water}}^e = V \times \left(1 - \frac{U_{\text{Na}} + U_{\text{K}}}{P_{\text{Na}}} \right). \quad (2.10)$$

From (2.10), it follows that a positive electrolyte-free water clearance occurs when the plasma sodium concentration exceeds the sum of urinary sodium and potassium concentrations. In such a setting, the urine is hypotonic relative to plasma (even if its total tonicity is greater than that of plasma), and if the urinary losses are not matched by appropriate hypotonic water intake, then the resultant negative free water balance causes an increase in the serum sodium concentration. Conversely, when the urinary concentrations of sodium and potassium exceed the serum sodium concentration, then the electrolyte-free water clearance becomes negative, reflecting the reabsorption of free water. This setting results in the excretion of hypertonic urine, and the kidney's reabsorption of free water will decrease the serum sodium concentration.

Because hypotonic hyponatremia is *always* the result of relative water retention, the assessment of a hyponatremic patient's electrolyte-free water clearance using the above equation can be very useful in determining the kidney's role in the positive water balance. Very often, this approach will reveal a defect in urinary dilution as the cause of the hyponatremia. Alternatively, it may reveal appropriate urinary dilution, suggesting a different underlying cause of the hyponatremia.

Given the overall importance of the urinary diluting mechanism in preventing water retention, consideration of the nephron's various transport mechanisms and their hormonal control is essential in the understanding of the pathogenesis of hyponatremia. These specialized mechanisms throughout the nephron will be addressed below in sequential order and illustrated in Fig. 2.3.

Components of the Urinary Diluting and Concentrating Mechanisms

Glomerular Filtration and the Proximal Convuluted Tubule

Fine control over water balance occurs in the distal nephron, and as a result, adequate delivery of tubular fluid to that nephron segment is essential in allowing this tight regulation to occur. Under normal conditions, 70 % of the glomerular filtrate is reabsorbed isotonicly through the water-permeable proximal convoluted tubular epithelia. The remaining 30 % of the isotonic filtrate is essential to the loop of Henle's generation of a medullary interstitial tonicity gradient, which is ultimately required for distal water balance control. Because of the importance of this medullary tonicity gradient in the overall control of water balance (particularly in the process of urinary concentration), decreases in the amount of fluid leaving the proximal tubule can interfere with water balance regulation by preventing the proper establishment of the tonicity gradient. In addition, decreased tubular flow

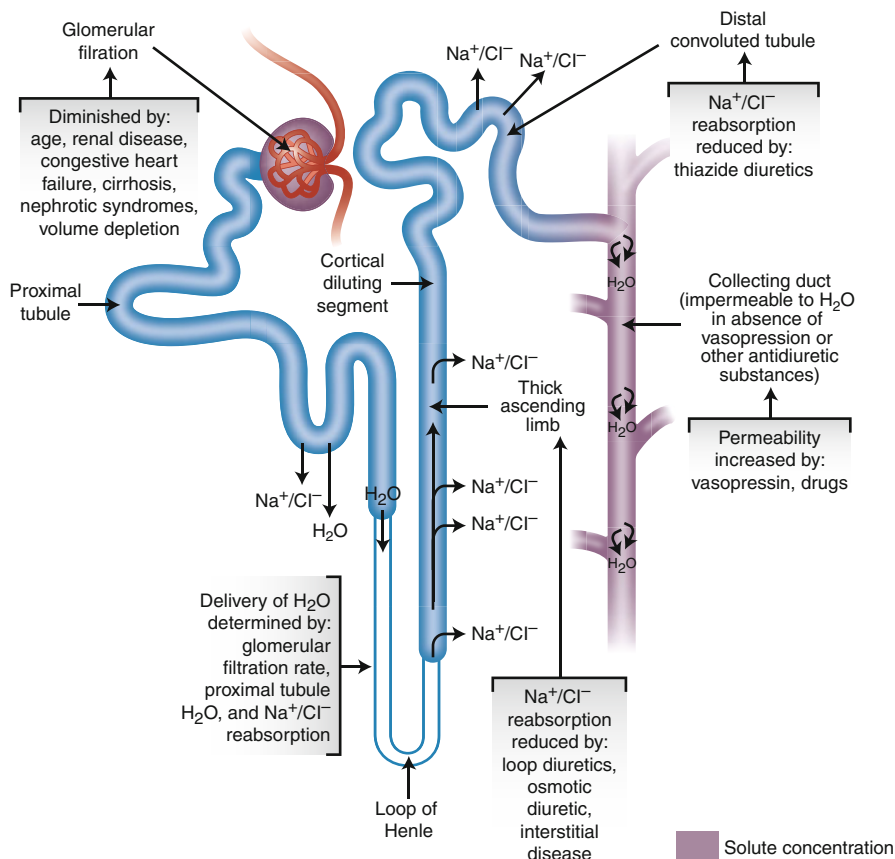


Fig. 2.3 Mechanisms of urinary dilution. The specialized mechanisms in each nephron segment that contribute to urinary dilution are shown, as well as the sites of impairment in urinary dilution that produce hyponatremia

can deprive the distal nephron of the substrate it needs to exert control over water balance and sets the upper limit of urine flow that can be excreted. These states of poor distal delivery can arise when the glomerular filtration rate (GFR) is decreased or proximal tubular reabsorption is increased; this combination is often seen in the setting of volume depletion or poor renal perfusion.

The Loop of Henle

As isotonic filtrate moves through the descending thin limb of the loop of Henle, water is reabsorbed through the aquaporin-1 water channel, causing progressive concentration of tubular fluid [3]. The degree to which the increase in the tonicity of

tubular fluid is contributed to by solute addition seems variable among species, but a component of urea addition probably also contributes to the process. Water reabsorption in this nephron segment is passive, driven by the increased medullary hypertonicity that results largely from high urea levels (which, in turn, result from inner medullary collecting duct urea reabsorption). Tubular fluid reaches its peak osmolarity of approximately 1,200 mOsm/L at the loop's hairpin turn, after which the concentrated tubular fluid begins its ascent through the water-impermeable thick ascending limb. Sodium reabsorption is probably passive in the thin ascending limb, but in the thick ascending limb, tubular fluid sodium, chloride, and potassium are reabsorbed through $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporters, while water remains in the tubular lumen. This process results in progressive dilution of the tubular fluid, until an osmolarity nadir is reached as the fluid enters the distal tubule with a tonicity of about 100 mOsm/L.

In addition to diluting the tubular fluid, solute reabsorption and water impermeability throughout the ascending limb also create a gradient of interstitial tonicity throughout the medulla, with increasingly higher tonicities at deeper levels of the medulla. This gradient is absolutely essential in the more distal and fine control over water balance exerted by AVP. Substantial decreases in the delivery of fluid to the loop of Henle due to low glomerular filtration rate (GFR) or increased proximal tubular reabsorption can impair the kidney's concentrating ability because this ability relies upon the ascending limb's ability to generate this medullary osmolarity gradient. In addition, the medullary hypertonicity gradient depends upon regulated blood flow through the hairpin configuration of the vasa rectae that supply the area [4]. Significant increases in the flow of blood through these vessels can partially dissipate the tonicity gradient and thereby diminish more distal water reabsorption.

The Distal Tubule and Collecting Duct

The delivery of hypoosmotic fluid to the collecting duct and the descent of the collecting duct through a progressively more hypertonic medullary interstitium provide a background in which fine control over water excretion can be exerted. At this point, the major determinant of urine osmolarity and water clearance is arginine vasopressin (AVP), a cyclic hexapeptide with an additional three amino acids, synthesized in the supraoptic and paraventricular magnocellular nuclei of the hypothalamus. Understanding the regulation and action of this hormone is vital for understanding the physiology of water balance and the pathophysiology of most hyponatremic states.

AVP is synthesized in the hypothalamus and stored in posterior pituitary secretory granules until its release is prompted by either osmotic or non-osmotic stimuli. The osmotic trigger for AVP release is mediated by osmoreceptor cells located in the organum vasculosum of the lamina terminalis and the subfornical organ. These cells sense ECF osmolarity through cellular swelling, and via their projections to the anterior hypothalamus and through activation of TRV4 channels, they trigger AVP

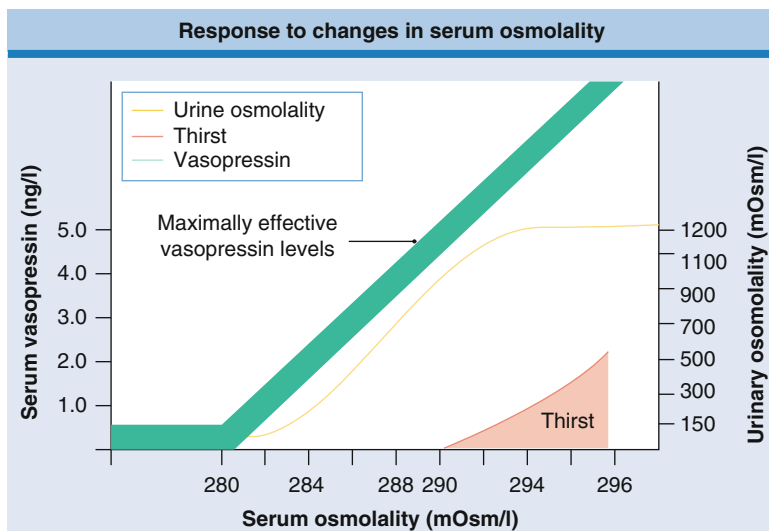


Fig. 2.4 Vasopressin levels, urinary osmolality, and thirst at different serum osmolarities. The levels of vasopressin, urinary osmolality, and thirst are shown in relationship to serum osmolality. (Adapted from Narins RG, Krishna GC. Disorders of water balance. In: Stein JH, editors. Internal medicine. Boston: Little, Brown; 1987, with permission from Elsevier)

release in response to an increase in ECF osmolality of as little as 1 %. In contrast, a 1 % decrease in ECF osmolality results in complete AVP suppression. In absolute terms, the window for AVP release is normally set between 280 and 290 mOsm/kg (Fig. 2.4). In light of the relationship between serum sodium concentration and osmolality, this osmotic set point for AVP release results in non-detectable plasma AVP levels when the serum sodium concentration is below 135 mEq/L, and AVP levels reach approximately 5 pg/mL when the serum sodium concentration is 140 mEq/L. Working properly, this system confines plasma osmolality and serum sodium concentration to a very narrow range.

More important in the consideration of hyponatremic states are the variety of non-osmotic stimuli for AVP release, the most important of which is decreased blood pressure or intravascular volume. Venous baroreceptors in the atria and arterial baroreceptors in the carotid arteries and aorta detect intravascular volume and blood pressure. In concert, these receptors will prompt AVP release when they perceive a decrease in blood volume or pressure, sending afferent signals to the brain through the vagus and glossopharyngeal nerves. The degree of decrement in intravascular volume or pressure that stimulates AVP release has been reported to be approximately 7 %. Because this stimulus for AVP release is involved in the defense against circulatory collapse, it is considerably stronger than the osmotic signals and will therefore prevail over any contradictory osmotic signals that may coexist. This discrepancy in the stimulus strength is of considerable importance when considering certain hyponatremic states, as described in the next section. It is also important to note that a variety of other non-osmotic stimuli for AVP release exist as well, including nausea, hypoglycemia, pain, and emotional stress.

Regardless of the source of its stimulation for release, circulating AVP exerts its influence over water balance in the collecting duct of the kidney. In the absence of AVP, the collecting duct is largely water impermeable, and thus, the hypotonic fluid that reaches the collecting duct will be excreted without significant tonicity changes as dilute urine. In the presence of AVP, however, urine tonicity will change dramatically. AVP binds to the V2 receptors on the basolateral membrane of collecting duct principal cells, resulting in translocation of aquaporin-2 (AQP2) water channels into the luminal membranes through a cyclic AMP signaling pathway [5, 6]. The resulting increased water permeability of the collecting duct causes passive water reabsorption down its concentration gradient into the hypertonic medullary interstitium. AVP's effect on collecting duct water permeability through this mechanism occurs within minutes and allows for rapid and short-term regulation of water clearance. However, it is also notable that when elevations in plasma AVP levels are sustained for longer than 24 h, the expression of AQP2 is increased, and the greater number of AQP2 channels available for translocation into the luminal membrane allow for even greater maximal water permeability in the collecting duct. This long-term regulation has been observed and likely has clinical relevance in the hyponatremias that can accompany the edematous disorders.

Through its short-term action on the water permeability of the collecting duct, AVP will decrease urinary free water clearance until the stimulus for its release from the pituitary is removed. Feedback cessation of AVP stimulation can occur when an osmotic stimulus is extinguished as a result of AVP-stimulated water reabsorption which will dilute a high serum sodium concentration and return serum osmolality to the normal range. Feedback in this system can also occur if water reabsorption improves any decreases in intravascular volume or pressure that may have caused a non-osmotic stimulation of AVP release.

Taken together, this feedback system allows for a relatively constant serum sodium concentration despite wide variations in water intake and significant changes in non-renal water losses. Practically speaking, an ingested water load will cause a drop in plasma tonicity that causes inhibition of AVP secretion, leading to a water diuresis that ultimately normalizes the decreased plasma tonicity. Conversely, plasma hypertonicity caused by water deprivation will stimulate AVP secretion, causing an antidiuresis, and the positive water balance and retention will dilute the plasma hypertonicity back to the normal range. The dynamic ability of the kidney to vary the tonicity of urine from roughly 50 mOsm/L to in excess of 1,200 mOsm/L allows accommodation of substantial variability in water intake and non-renal water loss, and this capacity has afforded the species with a tremendous survival advantage and flexibility as it evolved to meet the challenges of life on dry land.

While AVP plays a primary role in determining urine tonicity through its actions in the collecting duct, there also appears to exist an AVP-independent regulation of urinary concentration related to the rate of distal solute delivery. Specifically, urine osmolality has been shown to decrease as solute excretion increases. This urinary dilution may result from the fact that solute diuresis can cause increased medullary blood flow and therefore decreased medullary hypertonicity, which would in turn blunt the urine concentrating ability of AVP. Secondly, increased solute delivery produces rapid flow in the collecting duct that may not allow complete osmotic

equilibrium to occur between the tubular fluid and interstitium when AVP is present, thereby causing a more dilute urine than the AVP levels should dictate.

As mentioned above, both the input and the output side of water balance must be appreciated in understanding water balance physiology, so in addition to this consideration of renal water excretion, it is important to understand the complex control over water intake that is effected through the regulation of thirst. First and foremost, hypertonicity is known to be a potent stimulus for thirst as well as AVP release. The resultant increase in water intake acts in concert with the antidiuretic effect of AVP to restore normal tonicity. With regard to its role in regulating plasma osmolality, however, thirst control is less sensitive than AVP regulation and is complicated by a variety of other influences. Thirst stimulation occurs at a plasma tonicity approximately 10 mOsm higher than does osmotic stimulation of AVP release; [7] thus, a 2–3 % increase in plasma osmolality is required to stimulate thirst, in contrast to the 1 % increase required to stimulate AVP release. In fact, the osmotic set point for thirst stimulation roughly correlates with the point at which urine is maximally concentrated through AVP's action (Fig. 2.4), so increased water intake is prompted only when the kidney's ability to conserve water is nearly at its capacity, thereby serving as a second line of defense against severe hypernatremia. Secondly, thirst is influenced by factors other than osmolality, such as mouth dryness [8, 9], hypovolemia, hypotension, and angiotensin II. Additionally, thirst can be suppressed by oropharyngeal mechanoreceptors when they detect fluid consumption [10]. Unlike AVP's minute-to-minute control over urinary water excretion, these thirst control mechanisms do not reflect regulation of plasma osmolality per se but instead exist to prevent overcorrection of hyperosmolality, as gastrointestinal absorption of ingested water can take up to an hour. The defense against overcorrection is further bolstered by the fact that fluid intake rapidly causes a transient suppression of both thirst and AVP levels, significantly before any resultant drop in plasma tonicity [11, 12].

Taken together, control over thirst and the regulation of urine composition allow for substantial control over water balance despite wide variations in water intake and non-renal fluid losses. Maintaining this stability allows for a relatively constant plasma osmolality, and conversely, dysnatremias occur when this balance is disrupted. The pathophysiology of the hyponatremic disorders should be understood in light of these balance considerations.

Approach to the Patient with Hyponatremia

Introduction

Hyponatremia develops when water intake exceeds the body's ability to excrete urine that is sufficiently dilute to maintain strict water balance, resulting in net water retention. The underlying cause of the defect in urinary dilution is related

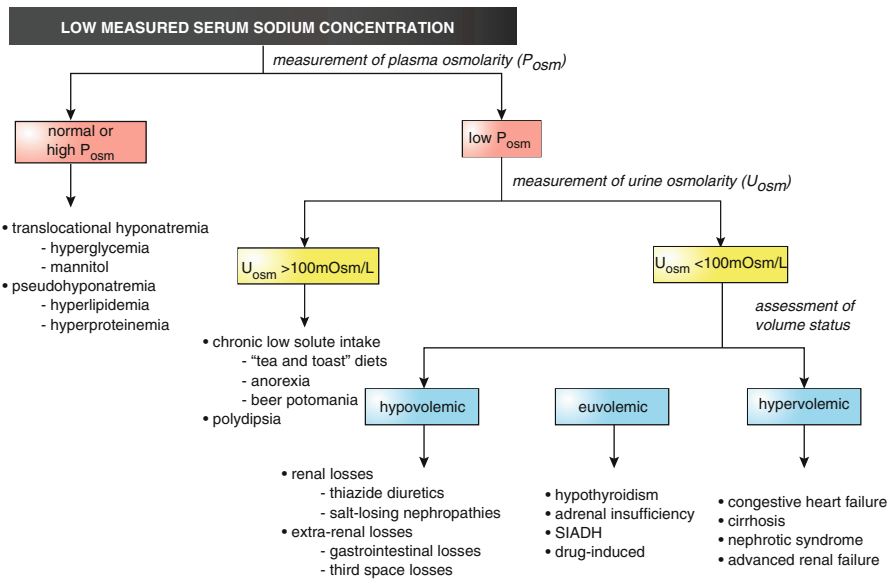


Fig. 2.5 Approach to the patient with hyponatremia. A general and systematic approach to the patient with a low measured serum sodium concentration

either to the secretion of AVP in response to non-osmotic stimuli or, in AVP's absence, to dramatic alterations in water and solute intake that prevent normal water balance from being maintained. A general approach to a low measured plasma sodium measurement is shown in Fig. 2.5.

Defining Hypotonic Hyponatremia

The first step in assessing a patient with a low reported serum sodium concentration is to evaluate whether this laboratory value represents hypotonic hyponatremia. Because sodium is the primary determinant of serum osmolality [13], true hyponatremia should be hypotonic in nature. However, there are settings in which low serum sodium values can occur in patients with normal or even high plasma osmolality.

The more common of these settings is that of translocational hyponatremia. In this circumstance, abnormally high concentrations of osmotically active particles are present in the serum and draw water from the intracellular compartment to establish osmotic equilibrium. The commonest solutes to cause this shift of water are glucose, mannitol, and glycine (which is often used as an irrigant during hysteroscopy, laparoscopy, or transurethral resection of the prostate or bladder). Hyperglycemia bears particular mention as translocational hyponatremia can be quite common in the setting of diabetic ketoacidosis and hyperosmotic hyperglycemic non-ketotic coma, and up to 20 % of

hospitalized cases of hyponatremia may result from concomitant hyperglycemia [14]. Theoretical calculations previously suggested that for every increase of 100 mg/dL in plasma glucose, the plasma sodium decreases by 1.6 mEq/L [15]. Later experimental work has shown that this is an underestimate; a correction factor of at least 2.4 mEq/L per 100 mg/dL of glucose appears to be more accurate [16].

In addition to these translocational hyponatremias, a phenomenon known as pseudohyponatremia can produce a low measured serum sodium concentration despite the absence of hypotonicity. Flame emission spectrometry assays plasma sodium concentration by quantifying the intensity of emitted light from a specific volume of plasma and translating that intensity into a concentration of sodium per unit volume of plasma. This calculation assumes that 7 % of the plasma volume is comprised of nonaqueous lipid and protein, which is true under normal circumstances. However, when the nonaqueous portion of plasma rises significantly, the measured plasma sodium concentration per unit of total plasma volume will be falsely decreased (although the concentration per unit of plasma water would not be). Pseudohyponatremia of this variety most commonly occurs in the setting of severe hyperlipidemia or hyperproteinemia; these disorders can reduce the aqueous phase of plasma from the usual 93 % of total plasma volume to below 75 % [17, 18]. Of note, the measured plasma osmolality in this condition will remain normal as a standard osmometer measures the tonicity of only the aqueous phase. Suspicion of pseudohyponatremia can be confirmed through the use of direct reading potentiometry with sodium selective electrodes on an undiluted sample, which will yield the accurate sodium concentration regardless of the proportion of plasma that exists in the nonaqueous phase.

Hypotonic Hyponatremia in the Setting of Dilute Urine

Once it has been verified that hyponatremia is occurring in the setting of plasma hypotonicity, the clinical approach commences with an evaluation of the urine osmolality. If urine is demonstrated to be dilute (i.e., with an osmolality of less than 100 mOsm/L), then the differential diagnosis is confined to polydipsia and states of low solute intake.

Polydipsia resulting in hyponatremia is a condition in which water intake exceeds the kidney's ability to excrete a sufficiently dilute urine despite intact diluting capacity. This disorder remains somewhat uncommon in patients with normal renal function because the normal kidney can excrete a volume of free water that is difficult to exceed through ingestion. To illustrate, consider that normally functioning kidneys are capable of achieving a free water clearance equal to roughly 20 % of the GFR. As such, a person with a GFR of 100 mL/min can excrete over 25 L of free water per day. Achieving positive water balance in this setting would then require the subject to ingest over 25 L of water in a day, which is a difficult feat.

However, while ingesting above the kidney's daily water excretion capability is difficult, exceeding the hourly rate of urinary free water clearance is more attainable on a short-term basis. The kidney rarely excretes more than 1 L of water per hour, so excessive water drinking over a short period of time can lead to transient positive water balance. Of course, for the resulting hyponatremia to persist, the excessive water ingestion must be sustained; once it ceases, then the full suppression of AVP release will result in the rapid excretion of the excess free water and the swift resolution of the transient hyposmolarity.

From the above discussion, it follows that exceeding the kidney's ability to clear free water is easier to achieve when GFR is decreased, as maximum water clearance would be diminished and therefore positive water balance would occur at lower volumes of ingestion. Still, sustained hyponatremia due to polydipsia can occur in patients with normal GFR, albeit rarely. One setting where this disorder is particularly notable is in institutionalized psychiatric patients with schizophrenia [19, 20]. Compulsive water-drinking behavior has been reported in up to 6 % of such patients [21]. It is speculated that some of these patients have a central defect in thirst regulation [22] and may have lower osmotic set points for thirst stimulation than they do for ADH release [23], leading to their excessive water intake.

In these patients, it should be noted that excessive water intake is often only one contributor to the multifactorial hyponatremia. First of all, many patients with schizophrenia are prescribed psychiatric medications that enhance AVP release and stimulate thirst, thereby interfering with appropriate urinary dilution while also stimulating water intake. In addition, patients with schizophrenia have been shown to release AVP during episodes of acute psychosis [24, 25], allowing for positive water balance to occur with less profound polydipsia than would be required otherwise. AVP responsiveness in the kidney also appears to be more pronounced in these patients for reasons that are not entirely unclear [26]. Finally, the threshold for AVP release may be reset to a lower osmolarity in patients with schizophrenia.

Aside from the setting of schizophrenia and acute psychosis, polydipsia can result in hyponatremia in other clinical situations as well, although far less commonly. For example, patients with hypothalamic lesions or infiltrative diseases such as sarcoidosis that affect the brain's thirst control center can develop excessive water drinking that produces positive water balance [27].

Another setting in which hypotonic hyponatremia can occur is in the face of a dilute urine in states of prolonged low solute intake. In order to maintain daily balance, the average adult eating a normal diet must excrete roughly 800 mmol of solute per day (as described above), most of which is the result of dietary intake and nutrient metabolism. Assuming that maximally dilute urine has an osmolarity of 50 mOsm/L, these 800 mmol can be excreted in up to 16 L of urine. As such, neutral water balance can be achieved as long as the individual does not ingest over 16 L of water per day. However, in patients with severely low solute intake (e.g., anorectics or those on "tea and toast" diets), the maximum amount of dilute urine that can be excreted will be substantially lower because the obligate solute excretion is decreased. Accordingly, positive water balance can occur with significantly less water ingestion [28].

To illustrate, consider a patient who needs to excrete only 200 mmol of solute per day due to poor oral intake. With a maximally dilute urine of 50 mOsm/L, this patient can produce a maximum of 4 L of urine per day, a volume that is far easier to exceed through ingestion. Due to the extremely low solute content of beer and the high volume of this beverage that some patients consume, this situation can easily occur in when patients subsist on little food and excessive beer. The resulting hyponatremia has been termed beer potomania.

Hypotonic Hyponatremia in the Setting of Non-dilute Urine

Most patients with hypotonic hyponatremia produce urine that is not maximally dilute (i.e., U_{osm} exceeding 100 mOsm/L), and their hyponatremia reflects positive water balance primarily as a consequence of persistent AVP secretion. In some settings, this AVP release is stimulated by decrements in total blood volume. In others, the ECF volume may be expanded, but there is a decrement in *effective* arterial blood volume (EABV) that is involved in the pathogenesis of the hyponatremia.

Because the concept of EABV is central to understanding the pathogenesis of hyponatremia in a variety of conditions, a further explanation is warranted before proceeding. EABV refers to the volume of blood perfusing the peripheral tissues, and maintaining an adequate perfusion relies not just on the intravascular volume but also on cardiac output, peripheral vascular resistance, and oncotic pressure. Depending on the physiology of these other determinants, EABV can be significantly reduced even in the setting of ECF volume expansion. Central to the pathogenesis of hyponatremia in these conditions, diminished EABV can stimulate AVP release in the same way that true volume depletion does. In addition, both types of volume depletion produce alterations in renal hemodynamics that reduce GFR and enhance proximal tubular reabsorption, resulting in diminished delivery of fluid to the distal diluting segments of the nephron and thereby further limiting the volume of urine that can be excreted.

It should be noted that not all cases of hypotonic hyponatremia in the setting of non-dilute urine involve states of low EABV, but many of them do. The general approach to patients with hypotonic hyponatremia and non-dilute urine begins with an assessment of volume status.

Hypovolemic Hyponatremia

Hypovolemic hyponatremia arises when the total body sodium is decreased out of proportion to a decrease in the total body water. In this situation, the relative degree of water retention is responsible for the low serum sodium concentration. The non-osmotic release of AVP triggered by the fall in intravascular volume or pressure overrides the suppressive signals prompted by osmoreceptors that detect

hypoosmolality. This hierarchy of stimuli reflects what has been termed the “law of the circulating volume,” whereby the preservation of volume and defense of blood pressure takes precedence over the maintenance of tonicity.

There are a variety of potential sources of fluid loss that can produce hypovolemic hyponatremia. The concentration of sodium in the urine can suggest whether the fluid loss is renal or extra-renal in nature. In cases of fluid loss through the gastrointestinal tract or into the third space (e.g., in the setting of pancreatitis, bowel obstruction, or burns), the urinary sodium concentration will typically be low (i.e., <20 mEq/L) if renal function is normal, reflecting the sodium avidity that results from increased angiotensin II, aldosterone, and other sodium-retaining neurohumoral pathways. An exception to this low urine sodium is sometimes seen in cases of vomiting, in which metabolic alkalosis causes bicarbonaturia, which results in urinary sodium loss and a urine sodium concentration of >20 mEq/L. In this setting, a low urinary chloride (i.e., <10 mEq/L) can be a surrogate marker of sodium avidity.

The absence of markers of sodium avidity (i.e., a urine sodium >20 mEq/L without vomiting) suggests that hypovolemia is the result of urinary fluid loss instead. This situation is most commonly seen with diuretic use, which warrants further discussion given its frequency as a cause of hyponatremia in both inpatient and outpatient settings [29, 30]. The risk for diuretic-induced hyponatremia appears to increase with advancing age and decreasing body mass, and this phenomenon appears to be more common in women [31, 32]. The elderly may be at particular risk due to an age-related decrease in the ability to excrete a water load, a defect that is magnified in the presence of thiazide diuretics [33]. Hyponatremia typically occurs within the first 2 weeks of therapy [34].

Thiazides are virtually always the culprit in diuretic-induced hyponatremia. Unlike loop diuretics, thiazides interfere with solute reabsorption in the diluting segment of the nephron, preventing the kidney from generating a maximally dilute urine. In addition, diuretics can induce volume depletion, causing decreased distal fluid delivery and increased AVP release, and both of these consequences can contribute to hyponatremia in the setting of already impaired urinary dilution. Loop diuretics, in contrast, block solute reabsorption in the ascending limb of the loop of Henle, thereby diminishing the establishment of a hypertonic gradient throughout the medulla. As a result, even if a loop diuretic induces enough volume depletion to stimulate AVP release, the diminution of medullary hypertonicity limits the urinary concentration that AVP would otherwise mediate in the collecting duct, thereby counteracting free water retention and preventing hyponatremia [35].

Potassium depletion can also contribute to hyponatremia in the setting of diuretic use and intravascular volume depletion. Hypokalemia can induce an efflux of potassium from the intracellular compartment in order to replete the diminished extracellular store. To maintain electroneutrality, this potassium efflux is matched by extracellular sodium movement into the intracellular compartment. Sodium loss from the ECF can produce a drop in serum sodium concentration in the setting of volume depletion, when secondarily elevated AVP levels prevent the compensatory water diuresis that would otherwise normalize the serum sodium concentration.

The impact of hypokalemia on this type of hyponatremia is suggested by studies that show exogenous potassium chloride can improve the hyponatremia even in the absence of sodium repletion [36–38].

Other less common causes of renal solute losses that can cause hyponatremia through AVP stimulation include mineralocorticoid deficiency or resistance [39], adrenal insufficiency [40], osmotic diuresis, and salt-wasting nephropathy. This latter condition can arise in the setting of polycystic kidney disease [41] or interstitial nephritis [42].

Euvolemic Hyponatremia

Euvolemic hyponatremia results from an increase in total body water without a change in total body sodium. This form of hyponatremia is the most commonly encountered among hospitalized patients [14] and has a variety of potential causes that share a common underlying physiology—AVP release that is unregulated and unprovoked by either osmotic or non-osmotic stimuli. In this regard, the most well-recognized cause of euvolemic hyponatremia is the syndrome of inappropriate antidiuretic hormone (SIADH), which is the most common overall etiology of hyponatremia [43].

Syndrome of Inappropriate Antidiuretic Hormone

SIADH classically results from elevated AVP levels during conditions in which pituitary AVP release should be suppressed. A variety of etiologies may underlie this inappropriate AVP release, but regardless of the inciting cause, the elevated AVP levels result in urine that is inappropriately concentrated with respect to plasma tonicity, and this relative water retention dilutes the serum sodium concentration. These patients do not develop edema for two reasons. First, because two-thirds of total body water is retained in cells, water retention tends not to cause the ECF volume expansion that results in edema. Second, any significant water retention in the intravascular space will activate volume receptors that trigger a compensatory natriuresis that offsets any volume expansion. Of note, the resulting negative sodium balance can contribute somewhat to the hyponatremia [see (2.5)]. In the setting of persistently elevated plasma AVP levels, an escape from AVP-induced water retention may occur over time due to downregulation of AQP2 channels [44], but hyponatremia will still occur in this setting unless water intake is restricted.

SIADH is diagnosed by exclusion. Its diagnostic characteristics include hypotonic hyponatremia in the setting of clinical euvolemia and an inappropriately elevated urinary osmolality. These findings in a patient who is not taking diuretics or other drugs associated with hyponatremia should elicit a work up for other causes of euvolemic hyponatremia, with a strong suspicion for SIADH. A negative evaluation for these other conditions such as hypothyroidism and adrenal insufficiency allows an exclusionary diagnosis of SIADH to be made [45].

Once the diagnosis is made, an attempt to find the underlying cause of SIADH should be endeavored. Idiopathic SIADH is a relatively rare phenomenon but appears to be more common in elderly patients [46–48]. The observation that both hyponatremia in general and idiopathic SIADH in specific are more common among the elderly [49, 50] suggests that AVP regulation changes as people age. To that point, a higher sensitivity to osmotic stimuli has been demonstrated in older subjects [51]. Not surprisingly, therefore, there is evidence that hyponatremia is more common in older patients in general and as a hospital-acquired phenomenon as well [52]. Still, when overt SIADH is observed in any patient in the absence of obvious causes, an extensive and age-appropriate work up for occult malignancy should be made before the SIADH is labeled idiopathic, as hyponatremia is occasionally the presenting abnormality with certain cancers.

While true idiopathic SIADH is rare, secondary causes are more common. As alluded to above, malignancies are one of the most common causes of SIADH. Bronchogenic carcinoma of the lung, especially small-cell lung cancer, is one of the most frequent associations, with incidences reported up to 11 % overall [53] and 33 % in patients with more extensive disease [54]. Head and neck cancers are also commonly associated with SIADH [55], and cancers of the pancreas or duodenum are other reported associations. The mechanism of malignancy-related SIADH is often related to ectopic AVP production within the malignant tissue.

Central nervous system disorders such as hemorrhage, tumor, and infection are also frequent underlying processes for SIADH. These varied disorders can cause SIADH by stimulating excess AVP release from the pituitary, either by diminishing the tonic inhibition of AVP release or enhancing AVP-stimulatory pathways. Respiratory failure from a variety of pulmonary disorders (including acute pneumonia [56–58], chronic obstructive lung disease [59], and tuberculosis [60]) has been particularly associated with SIADH.

In addition to these broad categories of SIADH causes, the disorder has also been increasingly recognized as a complication in hospitalized patients with the acquired immunodeficiency syndrome (AIDS). Hyponatremia is seen in up to 38 % of AIDS patients, and SIADH has been reported as the etiology in up to 68 % of those cases [61]. Stress, pain, and postoperative status are also potential underlying causes of SIADH.

Irrespective of the cause of SIADH, four different patterns of AVP release have been described in SIADH [62]. In the so-called Type A pattern, AVP release occurs erratically and independently of plasma osmolality, and the dissociation between AVP levels and plasma osmolality results in osmotic dysregulation and consequent hyponatremia. Type B, or “reset osmostat,” bears similarity to normal AVP release patterns, in which a linear relationship exists between AVP and plasma osmolality. However, as compared to individuals with normal AVP release, patients with this type of SIADH have higher AVP levels for any given plasma osmolality. Like normal individuals, these patients have osmoreceptors that respond to changes in plasma tonicity, but their set point for AVP release is lower than normal. These patients suppress AVP in response to a water load and increase AVP in response to increased plasma tonicity, resulting in stable hyponatremia around the new

set point. Reset osmostat most commonly occurs during pregnancy [63–65] and can also be seen in patients with chronic malnutrition [66]. In addition, reset osmostat may contribute to the multifactorial hyponatremia seen in patients with psychosis [19, 26]. Urine in patients with reset osmostat can be dilute or non-dilute depending on their individual set point and their plasma tonicity. The Type C pattern of SIADH involves appropriate AVP release in the setting of normal or elevated plasma osmolality, but an inability to suppress AVP secretion beyond a certain level during water loading. The least common pattern, called Type D, involves an apparently normal relationship between AVP secretion and plasma osmolality but an increased sensitivity to the effects of AVP. Some of these type D patients may have gain-of-function mutations in the V2 receptor that result in so-called nephrogenic syndrome of inappropriate antidiuresis [67, 68].

Finally, medication-related hyponatremia is a particularly prominent cause of euvoletic hyponatremia, and the mechanism in many cases is stimulation of AVP release or potentiation of the renal action of AVP. In the former category, selective serotonin reuptake inhibitors are the most prominent, as well as carbamazepine, vincristine, and narcotics. The latter mechanism has been observed with chlorpropamide, cyclophosphamide, and nonsteroidal anti-inflammatory drugs.

Hyponatremia in Endocrinopathies

In addition to SIADH, a variety of less common causes of euvoletic hyponatremia also exist. Of note, hyponatremia is often seen in patients with primary adrenal insufficiency particularly when in the midst of an Addisonian crisis. Animal models involving AVP gene mutations and/or surgical adrenalectomies have helped elucidate the roles played by both mineralocorticoid deficiency and glucocorticoid deficiency in sodium and water homeostasis.

The mineralocorticoid deficiency seen in some cases of adrenal insufficiency can produce enough renal sodium wasting to cause hypovolemia and consequent non-osmotic AVP release, resulting in a hypovolemic type of hyponatremia. This mechanism has been proven by studies in which the low serum sodium levels of mineralocorticoid-deficient animals can be corrected simply by reversing their negative sodium balance [69]. However, it has been shown that animals with hypopituitarism can develop hyponatremia as well, despite the fact that this condition does not involve mineralocorticoid deficiency. This observation points to a separate role of glucocorticoid deficiency in the hyponatremia of adrenal insufficiency, and the pathogenesis of this hyponatremia is multifactorial.

There is evidence that glucocorticoids have a direct inhibitory effect on AVP expression in magnocellular neurons and are therefore required for complete suppression of AVP. As such, glucocorticoid deficiency removes the normal, tonic inhibition of AVP release and therefore results in inappropriately non-suppressed AVP levels in settings of normal plasma tonicity, leading to hyponatremia [70]. Second, AVP release can be further stimulated by the baroreceptor pathway that detects the decreased cardiac output and blood pressure that can accompany

glucocorticoid deficiency [71]. Third, in addition to these AVP-related mechanisms, AVP-independent factors exist, as a diluting defect is seen in genetically AVP-deficient, surgically adrenalectomized animals [72] and is fully corrected by steroid replacement [73]. A possible explanation for this observation is that glucocorticoid deficiency has been associated with increased collecting duct AQP2 expression [74], suggesting that glucocorticoids are required to render the collecting duct water impermeable. Taken together, glucocorticoid deficiency can result in hyponatremia with an elevated urine sodium concentration that is difficult to distinguish from SIADH but that will improve with glucocorticoid replacement alone.

Euvolemic hyponatremia may also complicate hypothyroidism, particularly in cases of severe primary hypothyroidism with myxedema [75, 76]. The proposed mechanism of this hyponatremia is related at least in part to non-osmotic AVP release due to poor cardiac output, as well as increased AQP2 expression in the collecting duct [77]. This hypothesis is supported by animal models of severe hypothyroidism as well as the observation that hypothyroid patients may fail to suppress AVP fully when water-loaded [78]. However, other factors are likely involved as decreased perfusion alone would likely cause significant sodium avidity, and the urine sodium concentration in this condition is not necessarily low [79]. As such, it is speculated that alterations of renal hemodynamics are also involved in the pathogenesis of this hyponatremia, and studies in surgically hypothyroid animals with congenital AVP-deficiency have suggested AVP-independent effects related to systemic and renal hemodynamics [80]. Thyroid hormone replacement has been shown to improve water excretion both in experimental models and in patients with this condition [77].

Exercise-Associated Hyponatremia

Exercise-associated hyponatremia has been the subject of some recent interest. This type of hyponatremia, an occasional complication of extreme exercise events like marathons and ultramarathons, can be associated with significant morbidity and mortality. The pathogenesis is felt to be multifactorial. First, significantly increased water intake is an essential component to the development of hyponatremia [81]. Positive water balance results from the concurrence of this increased water intake and submaximal urinary dilution, which results from the non-osmotic AVP release stimulated by the exercise itself [82] and the nausea [83], pain [84], and hypoglycemia [85] that can accompany it. This so-called inappropriate AVP release can be augmented by “appropriate” AVP release if hypovolemia has occurred due to sodium losses in sweat. Taken together, the concurrent excess water intake and impaired urinary dilution result in positive water balance and hyponatremia, occasionally with fatal consequences. Accordingly, investigators have identified the following features associated with hyponatremia in marathon runners: consumption of over 3 L during the marathon, ingestion of fluids at every mile of the race, racing time over 4 h, female gender, and low body mass index [86].

Hypervolemic Hyponatremia

Finally, hypervolemic hyponatremia occurs when there is an increase in both total body sodium and water, with the retention of water occurring out of proportion to the sodium retention. This disorder is primarily seen with the edematous states (especially congestive heart failure and cirrhosis), and the degree of hyponatremia can serve as a marker for the severity of the underlying disorder as well as a prognostic indicator. The pathogenesis of hyponatremia in these conditions is related to the hormonal and intrarenal consequences of low EABV [87].

Advancing congestive heart failure (CHF) is often associated with hyponatremia [71, 88] and is a marker for poor prognosis [89]. Cardiopulmonary congestion and low left-sided cardiac output result in arterial underfilling, which is sensed by mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles [90]. Activation of these mechanoreceptors produces increased sympathetic outflow and activation of the renin–angiotensin–aldosterone system, and these pathways lead to decreases in GFR and increases in proximal tubular reabsorption. The consequences of these changes are decreased water delivery to the distal nephron and interference with the establishment of a medullary interstitial tonicity gradient, therefore impairing free water clearance. Activation of those mechanoreceptors also leads to non-osmotic stimulation of AVP release and increased thirst, which produce hyponatremia as AVP interferes with urinary dilution while increased thirst sensation causes increased water intake. Additionally, AQP2 expression has been shown to be increased in animal models of advanced CHF [91], allowing for even greater water reabsorption in the presence of AVP. The frequent use of diuretics in this setting can further lower the EABV and thereby contribute to the hyponatremia.

Cirrhosis is another common setting in which hypervolemic hyponatremia can be seen [71]. Vasodilation in both the splanchnic and peripheral circulation result in low EABV. As in CHF, this fall in EABV is detected by mechanoreceptors and leads to a similar cascade of neurohumoral pathway activation that culminates in non-osmotic AVP release, increased thirst, and decreased distal delivery of fluid, all of which produce hyponatremia. High AVP levels have been demonstrated in cirrhotic humans [92], and animal models have demonstrated upregulated AQP2 in cirrhosis as well [93]. AVP-independent mechanisms have also been proposed in cirrhosis-related hyponatremia. As in CHF, the concomitant use of diuretics can exacerbate the situation by further reducing EABV.

Hypervolemic hyponatremia has been reported in the nephrotic syndrome as well, but the presence of hyponatremia in this condition is inconsistent and appears to be unrelated to disease severity. Some investigators feel that patients with severe urinary protein loss may lose enough oncotic pressure that they have diminished EABV, leading to hyponatremia through the neurohormonal mechanisms described above. However, there is disagreement on whether this physiology truly occurs in all patients with the nephrotic syndrome, particularly those with lower glomerular filtration rate in which the vasculature may be expanded.

Patients with renal failure (either acute or chronic) also can develop hypervolemic hyponatremia; [14, 94] a recent report showed a 15 % prevalence of hyponatremia in patients with CKD [95]. In renal failure, the increased solute clearance burden placed on each remaining nephron creates an osmotic diuresis that causes the minimal urine osmolality to rise from 50 mOsm/L to as high as 250 mOsmol/L despite suppression of AVP [96]. This dilutional impairment allows these patients to drink in excess of their maximal free water clearance capability more easily. It is important to note that patients with advanced renal failure often have high measured plasma osmolality because of high blood urea nitrogen levels. However, their hyponatremia can still be considered hypotonic in nature because urea is an ineffective osmole due to its free membrane permeability, and therefore, hyponatremia in these patients is associated with a low effective plasma osmolality.

As mentioned above, in addition to the non-osmotic stimulation of AVP release causing hyponatremia in these edematous disorders, hyponatremia can also be related to the diminished distal delivery of fluid that results from decreased GFR and increased proximal tubular reabsorption. While the diminished EABV at the root of this physiology should also result in renal sodium avidity due to secondary hyperaldosteronism, the measured urine sodium will not necessarily be low, as concurrent diuretic use is common, and urine sodium conservation can be interrupted by acute kidney injury and proximal tubular dysfunction in this setting.

Conclusion

The physiology of water balance involves a complex system of transport processes in the kidney and the tight hormonal control of water excretion that acts in concert with those mechanisms. Maintenance of strict water balance is essential in keeping the serum sodium concentration stable, and this regulation in turn produces a stable plasma osmolality. The importance of this stability is evident when water balance mechanisms are disrupted, and the pathophysiology of hyponatremia can be understood with respect to these water balance considerations. Using these concepts, a systematic approach to laboratory results showing low serum sodium concentrations will allow for an understanding of the underlying processes and will assist in formulating a treatment approach for this widespread clinical problem.

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