Physiologic basis for understanding quantitative dehydration assessment\textsuperscript{1–4}

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ABSTRACT
Dehydration (body water deficit) is a physiologic state that can have profound implications for human health and performance. Unfortunately, dehydration can be difficult to assess, and there is no single, universal gold standard for decision making. In this article, we review the physiologic basis for understanding quantitative dehydration assessment. We highlight how phenomenologic interpretations of dehydration depend critically on the type (dehydration compared with volume depletion) and magnitude (moderate compared with severe) of dehydration, which in turn influence the osmotic (plasma osmolality) and blood volume–dependent compensatory thresholds for antidiuretic and thirst responses. We also discuss the recent application of biological variation analysis to osmotic responses during dehydration for its novel potential as an adjunct (17) to clinical decision making.

INTRODUCTION
Dehydration (body water deficit) is a common physiologic state that can have profound implications for human health (1–7) and performance (8). Although mild dehydration can be easily corrected and is principally associated with impaired physical performance (8), it may be linked with common public health disorders if left chronically untreated (9, 10). A greater severity of dehydration can result in significant medical costs, morbidity, and mortality across the life span (11, 12). Although the physiology of osmotic and vascular volume responses to dehydration in humans have been well described (13, 14), the phenomenology of dehydration assessment has not. For example, there is no single, universal gold standard method of dehydration assessment for clinical decision making (7, 15, 16), which contributes greatly to the difficulty that clinicians encounter when trying to accurately assess dehydration in practice (17–25). This discordance between the physiology and phenomenology of dehydration is a recognized source of clinical confusion (17) for which clarity is needed to improve the practice of dehydration assessment.

In this review, we highlight how phenomenologic interpretations of dehydration depend critically on the type (dehydration compared with volume depletion) and magnitude (moderate compared with severe) of dehydration, which, in turn, influence the plasma osmolality (Posm)\textsuperscript{5}– and blood volume (BV)–dependent compensatory thresholds for antidiuretic and thirst responses. We also discuss the recent application of biological variation analysis to osmotic responses during dehydration for its novel potential as an adjunct (17) to clinical decision making.

Posm is the primary focus of this review because it is the key regulated variable in fluid balance (13, 14, 26–28), and it is commonly used to screen for dehydration and complement more quantitative differential diagnoses of dysnatremias and other diseases (3, 5, 28–30). The osmolality of other body fluids commonly used to assess dehydration (ie, urine and saliva) are also mentioned as is the practical assessment of volume depletion. Descriptions of other potential methods of dehydration and volume-depletion assessment have been provided by other authors (7, 16, 19, 31, 32). Complementary reviews (33) are similarly suggested for detailed information related to sodium (natriuresis and appetite) and nonosmotic contributors (eg, baroreceptors) to osmotic homeostasis.

FUNDAMENTALS OF OSMOTIC RESPONSES TO DEHYDRATION IN HUMANS
In its simplest form, the net body water balance is generally the zero sum of food (water and solute) and fluid intake minus insensible and obligatory renal water losses (7). Fluid intakes,
losses, and needs vary widely in free-living people and are governed heavily by physical activity, environmental stress, and cultural and habitual cues (7, 8, 34–36). Under conditions of ordinary daily body water flux, osmotic constancy is maintained by the secretion of the antidiuretic hormone arginine vasopressin (AVP), which directly influences renal water excretion and conservation in response to intravascular fluid shifts (that result from thermal and positional changes) and ad libitum food and fluid intakes (14, 26, 37–39). Thus, Posm remains stable as the kidneys modify urine osmolal and water excretion in accordance with ordinary living conditions. When a body water deficit in excess of ordinary flux occurs (dehydration), threshold increases in Posm (primary) and decreases in BV (secondary) produce compensatory water-conservation (renal) and water-acquisition (thirst) responses (14, 26). As a result, the discriminatory power of renal excretion measures for the detection of dehydration is always secondary to changes in Posm (28).

AVP is synthesized in supraoptic and paraventricular nuclei of the hypothalamus and is released from the posterior pituitary (14, 26). Basal AVP concentrations can fluctuate considerably in response to ordinary postural and skin-temperature (skin blood flow) shifts in BV (39). However, a threshold reduction in BV >10% is required to elicit greater (compensatory) AVP secretion, whereas smaller reductions in BV primarily act to enhance the sensitivity of the AVP response to changes in Posm (40–42). Osmotic homeostasis (<1–2% deviation in Posm) is also maintained by basal AVP regulation, but compared to BV smaller threshold increases in Posm (>2%) produce intracellular dehydration and compensatory increases in AVP secretion, renal water conservation, and thirst (14, 43).

When the net balance between water intake and output becomes negative (dehydration), renal water conservation is insufficient to restore fluid balance. Obligatory renal water losses persist, and fluid acquisition must occur, to restore the body water balance (28, 44). However, the Posm threshold for thirst is highly variable in people (27, 45, 46), and thirst mechanisms are subject to numerous influences unrelated to the body water balance (47). In humans, fluid losses (because of sweating, vomiting, or diarrhea) can easily outpace oral intakes. Peripheral osmoreceptors (eg, gut) (14) and oropharyngeal cues trigger thirst (14, 26, 37–39). As a result, the discriminatory power of renal excretion measures for the detection of dehydration is always secondary to changes in Posm (28).

Caveat 1: a sufficient body water–deficit threshold must be reached before compensatory reactions become reliably engaged

Percentage reductions in body mass (Bm) that exceed typical human variation are depicted in Figure 1, whereby a change in Bm is equated with a change in total body water (TBW). The change in Bm is used as the criterion value for practical purposes but also because the random measurement error for tracer-dilution methods (the change in TBW) is larger than the same for Bm (52). Typical human variation is defined as the day-to-day CV in Bm, which is <1.0% when fluid intake and activity are tightly controlled (53, 54). As a consequence, day-to-day change in Bm must exceed 1% and approach 2% (ie, \(\sqrt{2} \times 1.65\)) to be considered truly atypical (\(P < 0.05\); 1-tailed test). Therefore, day-to-day fluctuations in Bm <1–2% cannot be reliably associated with perturbations in body water beyond ordinary (sinusoidal) physiologic and behavioral body water regulation (55). Under these circumstances, renal water excretion or conservation is a reflection of the flux produced by fluctuating AVP concentrations in response to widely ranging dietary fluid intakes, osmolar loads, and ordinary compartmental fluid shifts without discernible changes in TBW, Posm, or, by extension, intracellular hydration (26, 37–39, 56). Thus, day-to-day fluctuations in Bm or TBW within this range should be interpreted as euhydrated (the state of normal hydration).

Caveat 2: body water–deficit threshold for dehydration depends critically on the type and magnitude of the body water deficit incurred

A 2% increase in Posm (~5 mmol/kg) and a 10% decrease in BV (~0.5 L) are commonly quoted physiologic thresholds for compensatory water conservation and acquisition (Figure 1) (26, 40, 43). Posm increases to greater than ~5 mmol/kg in response to dehydration via sweat losses, fluid restriction, or osmotic diarrhea (hypertonic hypovolemia) when those losses exceed ~2% of Bm (1.4 L at 70 kg) (18, 54, 57–59), which is a threshold that is also consistent with negative physiologic outcomes (7, 8, 60). The variation in sweat sodium losses in people may (61) or may not (62) add uncertainty to the magnitude of the osmotic response to a given water deficit, depending on the delicate balance between sweating rate and sweat sodium concentrations, whereby

$$\text{Volume} \times \text{concentration} = \text{content}$$

Similar considerations may be made of alterations in extracellular volume [plasma volume (PV)], but on the basis of the regression equations shown in Figure 2, the anticipated decrease in PV is only ~0.14 L at ~2% dehydration (63) because of the rapid osmotic redistribution of water from the intracellular to the extracellular (interstitial and intravascular) fluid compartment (61, 64). Therefore, hypertonic hypovolemia results in a small ratio of plasma-to-TBW losses (~1:10). Hypertonic hypovolemia would not produce intravascular volume losses >10% of BV until a 7% loss of Bm was achieved (Figure 2) (63, 65). This effect illustrates the primary influence of Posm as the stimulus for early compensatory water-conservation and -acquisition responses (40–42). Although the osmolalities of other body fluids (eg, urine and saliva) also increase in parallel with Posm and afford a good diagnostic accuracy for dehydration under ideal circumstances (54), they remain secondary (25) and are inferior to Posm for the detection of dehydration for additional reasons.

Isotonic hypovolemia can occur in response to diuretic use, cold or altitude exposure, secretory diarrhea, and vomiting (6, 18, 42, 44, 63, 65–68). The ratio of PV-to-TBW loss is approximately twice as large (~1.5) with isotonic hypovolemia than with hypertonic hypovolemia (63, 65, 68). This type of body water loss is often referred to as salt-depletion dehydration (44).
or volume depletion (24, 30) because the added solute loss produces little change in Posm but proportionally greater PV reductions. When there are large losses of solute from the extracellular space, there is a minimal or no osmotic gradient to pull fluids from the larger intracellular space (61, 64). As a result, a smaller ~4% loss of Bm (2.8 L at 70 kg; 0.56-L PV loss) must be incurred to achieve the 10% BV threshold for compensatory water conservation and acquisition with isotonic hypovolemia (Figures 1 and 2).

Methods for the assessment of volume depletion vary widely, with no single, standard approach advocated in the medical or related literature (16, 19). The use of a simple 20-beats/min sit-to-stand heart-rate response provides high specificity but low sensitivity and only marginal diagnostic accuracy even when dehydration is severe (65, 69). PV losses >10% (~1.0 L), whether measured directly (70) or by using lower body negative pressure to simulate equivalent blood losses (71), are required for an improved test sensitivity. The type of water loss with a gastrointestinal illness can be unpredictable or mixed (18, 44), and thus, the presence of both types of dehydration probably explains much of the difficulty associated with their interpretation (30, 44), in which neither Posm nor BV thresholds for compensatory responses are reached (Figure 1). Under these circumstances, a more heuristic assessment approach is needed (19, 22, 24, 28).

**BIOLOGICAL AND METHODOLOGIC VARIATION**

Human variation in osmotic responses to dehydration is primarily biological, but the methodology used to study osmotic responses can also contribute to variation. An understanding and appreciation for these sources of variation can inform probabilistic decision making related to the diagnosis of dehydration (54, 58, 72) and, likely, volume depletion as well (65).

**Threshold and slope of AVP and thirst responses (biology)**

It is common to refer to both the threshold and slope of the Posm-AVP relation. The threshold Posm value is associated with the initial increase in AVP secretion above baseline, whereas the slope is the responsiveness (or sensitivity) of the AVP system for
any given increase in Posm above the threshold value. The osmotic control of AVP, when defined by using slope and sensitivity terms, is highly variable. For example, there appears to be a polygenic basis for the variation in the slope of the AVP-Posm relation and Posm thresholds for AVP and thirst (46). The relations are highly correlated between monozygotic, but not dizygotic, twin pairs (46). For a healthy and heterogeneous population, the individual AVP-Posm slopes vary 10-fold in individuals but are highly correlated within a subject (r = 0.94). The osmotic threshold for AVP varies less in individuals (~ 8 mmol/kg) but shows only a moderate correlation within subjects (r = 0.61).

The individual variation of Posm set points and thresholds for both AVP release and unequivocal thirst relative to what has been commonly reported in the literature for group means is illustrated in Figure 3 (27). The variation contains the potential influences of sex (73), but not age (74), on osmotic responses. Posm thresholds for AVP release and unequivocal thirst differ in subjects by ~ 10 mmol/kg. The largest difference between Posm thresholds for AVP release and unequivocal thirst within an individual was 17 mmol/kg (subject 5). Also of importance is the difference in the Posm set point relative to the Posm threshold for AVP release and unequivocal thirst; for example, subjects 7 and 15 fell on opposite extremes. Taken together, the data in Figure 3 show that plasma osmotic responses (AVP and thirst) vary considerably in people and have a strong genetic component. These data may partly explain the 20-mmol/kg range in Posm often reported for population reference intervals (eg, 280–300 mmol/kg). Differences in health and hydration states must also contribute to this range, but the volume of fluid ingested and its proximity to measurement can also make an important methodologic contribution (43, 75), even in well-controlled laboratory situations.

Threshold and slope of AVP and thirst responses (methodology)

Some of the variation in the Posm threshold for AVP and thirst is methodologic rather than physiologic. In this context, moderate water loading is one methodology used to standardize Posm and suppress AVP secretion before imposing an intervention such as saline infusion or water restriction (dehydration). However, this approach produces low basal Posm values and results in threshold and slope calculations dissimilar from studies in which ad libitum water consumption was permitted before testing (13, 43, 45, 76). Suppressed Posm thresholds for AVP release and thirst in studies that used water-loading methodologies, although experimentally sound, may be unrealistic for free-living people.

Interpreting osmotic responses after water loading should be approached with caution. For example, the application of regression equations for AVP-Posm and AVP-urine osmolality (Uosm), which has been commonly adopted to explain the physiology of osmotic responses, indicated that a near maximally concentrated urine (~ 1100 mmol/kg) should occur at a Posm of 292 mmol/kg and AVP value of 4.6 pg/mL (43). This result contrasts with everyday observations but is easily understood from a starting Uosm:Posm ratio of approximately

\[\text{Uosm} = \frac{250 \times 0.35 \times \text{Posm} - 0.12 \times \text{Posm}}{1050 \text{ Uosm}} \] (3)

\[\text{Uosm} = \frac{250 \times 0.35 \times \text{Posm} - 0.12 \times \text{Posm}}{1050 \text{ Uosm}} \]

Therefore, both aspects of osmoregulation (ie, the variation and basal set point) are very important considerations when Posm is used to assess dehydration. When a person’s true Posm baseline is not known, biological variation analysis can provide confident probabilistic estimates of dehydration by using both single and serial measures of Posm.
Biological variation of Posm (single measure)

Claude Bernard’s concept of the tightly regulated milieu intérieur is commonly referenced by extension as a narrow 1–2% variation in Posm. Surprisingly few studies have quantified the intraindividual variation in Posm from day to day, but they have been consistent with this concept and reported values that ranged from 0.8% to 1.4% (2–4 mmol/kg), with the exclusion of the analytic (measurement) variation (~0.5% or 1 mmol/kg) (54, 78, 79). These studies (54, 78, 79) were not stratified and, thus, included contributions to the variation because of sex (73) and age (74). Although most measures of physiologic interest have a larger interindividual variation than intraindividual variation (80), the 2 measures are similar for Posm. This outcome seems to contrast with wide population reference intervals until it is considered that the variation between subjects shrinks when measurement methodology and other preanalytic factors are controlled for (80). The ratio of intraindividual to interindividual variation (index of individuality) in Posm ranges from 0.9 to 1.4 (54, 78, 79). The index of individuality provides a statistical framework to distinguish pathologic states such as dehydration from a single measurement. Any atypical value for a given individual, relative to the larger population of individuals, will go unnoticed when the ratio is <0.6 but will be captured when the ratio is >1.4 (80, 81). The probability of identifying an atypical value increases rapidly as the ratio exceeds 0.60 and approaches unity (1.00) (81).

The index of individuality concept for Posm is shown in Figure 4 and includes Uosm and saliva osmolality (Sosm) for comparison (54, 58). The interindividual variation is depicted by the differences in means (dots), whereas the intraindividual differences (typical day-to-day variation) in body fluid measures are represented by the range (bars) that surrounds each individual mean. “X” values in Figure 4 represent body fluid measures in response to a −2.5-L loss of body water (−3% dehydration). When graphed relative to the respective dehydration thresholds determined empirically by receiver operating characteristic curve analysis, probabilities of false-negative and -positive findings become apparent. The index of individuality for Posm was 0.90. For contrast, ratios for Uosm and Sosm were 0.49 and 0.27, respectively (54). As illustrated in Figure 4, an atypical value for Posm (X, dehydrated) is more easily and accurately detected than an atypical value for Uosm or Sosm, despite the expected linear associations commonly reported when the dehydration level against Sosm or Uosm is regressed. The complete biological variation analysis (54) supports a Posm threshold of 301 ± 5 mmol/kg, which is mathematically identical to the −0.56°C depression in the freezing point proposed by Olmstead et al (82) >50 y ago as a positive test for hypernatremia. We recommend the inclusion of a variance term (~5 mmol/kg) to account for biological differences in basal set points (54) and note its consistency to values (295–300 mmol/kg) reached by consensus (24) as consistent with impending dehydration.

Biological variation of Posm (serial measures)

Reference change values (80) allow the observation of serial changes in Posm to be interpreted in terms of diagnosing dehydration (54, 58). Reference change values can be calculated (when the proper statistical assumptions are met) (80, 83) by using the sum of analytic and intraindividual variations in Posm (80). The probability that a measured change in Posm is atypical can then be determined (58, 80). As illustrated in Figure 5, atypical changes in Posm begin above the daily 2–4 mmol/kg constancy threshold and provide increasing predictive certainty that dehydration has occurred in accordance with the equation

\[
\text{Probability} = 1 - e^{-0.327x}
\]

where \(x\) is the measured change in Posm (58). As a result, the probability that a change in Posm reflects the occurrence of dehydration can be gauged in both quantitative and qualitative terms.
osmolality. Posture (42, 92) and even low-intensity exercise (91). In contrast, simple changes in diet can affect Posm because of the osmolar shift of water out of the vasculature and into the gut (91). For example, consumption of a large meal can increase Posm.

Fluctuations in the volume of body fluid compartments will also affect Posm. For example, consumption of a large meal can increase Posm because of the osmolar shift of water out of the vasculature and into the gut (91). In contrast, simple changes in posture (42, 92) and even low-intensity exercise (40–60% maximal oxygen uptake) (93, 94) produce little effect, probably because osmotic concordance is not disrupted by the 2-way fluid flow between interstitial and intravascular spaces that share the same osmotic pressures (61, 64, 93). Higher exercise intensities increase Posm as a result of greater intravascular volume losses and the presence of lactic acid, but recovery appears complete in ~20–30 min (93). Finally, as stated earlier, Posm is of no use for the detection of volume depletion. When this distinction is made, coupled with the importance of biological variation and other issues discussed herein, criticisms for adopting Posm as a gold standard for dehydration assessment (15, 95–97) are minimal.

CONCLUSIONS AND FUTURE DIRECTIONS

Dehydration is a common physiologic state with implications for health and performance (1–8). Although the physiology of dehydration is well described, it remains difficult to assess accurately in practice. In this review, we highlighted how the phenomenologic interpretation of dehydration depends critically on the type and magnitude of dehydration, which directly affect threshold osmotic and volume-dependent compensatory anti-diuretic and thirst responses. We also emphasized how knowledge of biological variation improves our broader understanding of the physiology that underpins the osmotic response to dehydration in humans and affords important diagnostic insight for dehydration assessment. To help improve the practice of dehydration assessment, a single, atypical Posm threshold value of 301 ± 5 mmol/kg is suggested (54) as a starting point for this purpose, along with a nomogram (58) for the estimation of the probability of dehydration when serial changes in Posm are measured as an adjunct to quantitative differential diagnostic procedures. No standard method has been advocated for the assessment of volume depletion (16, 19), but a 20-beats/min sit-to-stand cutoff provides high test specificity for both dehydration and volume depletion (65, 69). Because Posm requires the collection of blood and the preparation of plasma, future efforts to identify or develop an acceptable noninvasive surrogate for Posm would benefit clinical, sports, and military medicine communities (7). A test with high diagnostic accuracy for moderate volume depletion is also needed.

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