Physiologic basis for understanding quantitative dehydration assessment

Samuel N Cheuvront, Robert W Kenefick, Nisha Charkoudian, and Michael N Sawka

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. In particular, we review new findings regarding the biological variation in osmotic responses to dehydration and discuss how this variation can help provide a quantitative and clinically relevant link between the physiology and phenomenology of dehydration. Practical measures with empirical thresholds are provided as a starting point for improving the practice of dehydration assessment.


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)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, compared with volume depletion) and magnitude (moderate compared with severe) of dehydration, which, in turn, influence the plasma osmolality (Posm)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.

1 From the US Army Research Institute of Environmental Medicine, Natick, MA.
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3 Supported by the United States Army Medical Research and Materiel Command.
4 Address correspondence to SN Cheuvront, Thermal and Mountain Medicine Division, US Army Research Institute of Environmental Medicine, Kansas Street, Building 42, Natick, MA 01760-5007. E-mail: samuel.n.cheuvront@us.army.mil.
5 Abbreviations used: AVP, arginine vasopressin; Bm, body mass; BV, blood volume; Posm, plasma osmolality; PV, plasma volume; Sosm, saliva osmolality; TBW, total body water; Uosm, urine osmolality.

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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. In particular, we review new findings regarding the biological variation in osmotic responses to dehydration and discuss how this variation can help provide a quantitative and clinically relevant link between the physiology and phenomenology of dehydration. Practical measures with empirical thresholds are provided as a starting point for improving the practice of dehydration assessment.
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 osmol 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 secre-
tion, 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 de-
hydration and compensatory increases in AVP secretion, renal
water conservation, and thirst (14, 43).

When the net balance between water intake and output be-
comes negative (dehydration), renal water conservation is in-
sufficient 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 osmo-
ceptors (eg, gut) (14) and oropharyngeal cues trigger thirst
satiation well before volume is fully restored (26, 48, 49), even
when dehydration is substantial (50). This transitory response
acts to buffer the presystemic impact of ingested fluids (14) but
often leads to involuntary dehydration when water is consumed
without food (solute) (47, 51).

TWO CRITICAL CAVEATS TO UNDERSTANDING
OSMOTIC RESPONSES TO DEHYDRATION

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 pur-
poses 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 fluc-
tuations 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 out-
comes (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 con-
centrations, whereby

\[
\text{Volume} \times \text{concentration} = \text{content}
\]  

Similar considerations may be made of alterations in extra-
cellular 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 intracellularextra-
cellular (interstitial and intravascular) fluid compartment
(61, 64). Therefore, hypertonic hypovolemia results in a small
ratio of plasma-to-TBW losses (~1:10). Hypertonic hypo-
volemia 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 sti-
mulus for early compensatory water-conservation and -acquisi-
tion 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 approxi-
ately 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).

**FIGURE 1.** Body water regulation in response to dehydration. Schematic includes the 2 major types of dehydration, their typical causes, and the estimated magnitude of dehydration required to stimulate a primary osmotic- or volume-dependent response for compensatory water conservation and acquisition (26). A change in TBW was equated with a change in body mass (1 L = 1 kg), whereby dehydration was expressed as a percentage of body mass in accordance with \( \Delta \text{body mass} / \text{body mass} \times 100 \). Plasma volume and TBW losses are depicted to scale as are their 1:10 and 1:5 ratios for hypertonic and isotonic hypovolemia, respectively. Dashed arrows represent negative feedback. Ang II, angiotensin II; AVP, arginine vasopressin; BV, blood volume; Posm, plasma osmolality; TBW, total body water.

**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

\[ \frac{187}{282} = 0.66 \] (2)

which can be back calculated from a starting AVP value of 1 pg/mL in these experiments (43). If we assume unity between plasma and urine electrolyte concentrations and accept that urea contributes 40% to Uosm (77), any Uosm:Posm ratio ≤1.5 is consistent with electrolyte-free renal water clearance and a water-loaded state (77). In contrast, the change in Posm (12 mmol/kg) that is responsible for the 1100-mmol/kg Uosm is entirely consistent with a hyposmolal state:

\[ \Delta Uosm = 250 \times 0.35 \Delta Posm \text{ or } A12 \text{ Posm} = \Delta 1050 \text{ Uosm} \] (3)

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.
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.

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

ubiquitous in simple terms. The equation (inset) describes the curved line and its

ability for dehydration. Semantic descriptors provide a scale that aligned

LIMITATIONS OF USE OF OSMOMETRY FOR

ASSESSMENT OF DEHYDRATION

It is clear that Posm is critical for body water regulation, and plasma is a unique body fluid for use in the assessment of dehydration. Although Uosm and Sosm have also been used successfully for this purpose (84, 85), human variation in these body fluids seem to limit their potential utility (Figure 4). The greater variation in Uosm and Sosm is not surprising. For example, ±40% of Uosm is attributable to urea (compared with only ~1% for Posm), and thus, the addition of solute in the form of antecedent diet or catabolic byproducts of protein metabolism associated with exercise or illness may increase Uosm by the addition of solute (86, 87). Similar limitations apply for urine-specific gravity, whereas all urine-concentration measures are subject to timing and uniformity concerns that manifest empirically as differences between first morning, 24-h, and spot urine measures (88) in addition to acute drinking and exercise behaviors (59). The discriminatory power of renal excretion measures for the detection of dehydration is clearly secondary to changes in Posm (28), but this does not, in any way, minimize the critical use of Uosm (and its relation to Posm) in the measurement of renal function related to the phenomenologic interpretation or differential diagnosis of other disorders (5, 28, 29). With regard to saliva, Sosm is subject to practical use issues related to simple oral artifacts (54, 89). Sosm may also be affected by anything that affects salivation (salivary flow), which includes a multitude of factors (85). Limitations of the use of Posm for the assessment of dehydration must also be acknowledged.

Posm and plasma tonicity (effective osmolality) are very similar quantities in health (90). However, substances in the blood that raise osmolality but not tonicity (ineffective or penetrating solutes) have the potential to confound dehydration assessment. The calculation of the osmol gap will reveal contributions from ineffective solutes, but the direct measurement of Posm is always recommended for dehydration assessment because of the large acceptable error in calculated osmolality (±10 mmol/kg) (90). 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% 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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