

Water-deficit equation: systematic analysis and improvement^{1–4}

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ABSTRACT

Background: The water-deficit equation $\{WD_1 = 0.6 \times B_m \times [1 - (140 \div Na^+)]\}$; B_m denotes body mass} is used in medicine and nutrition to estimate the volume (L) of water required to correct dehydration during the initial stages of fluid-replacement therapy. Several equation assumptions may limit its accuracy, but none have been systematically tested.

Objectives: We quantified the potential error in WD_1 for the estimation of free water (FW) and total body water (TBW) losses and systematically evaluated its assumptions.

Design: Thirty-six euhydrated volunteers were dehydrated (2.2–5.8% B_m) via thermoregulatory sweating. Assumptions within WD_1 were tested by substituting measured euhydrated values for assumed or unknown values. These included the known (premorbid) B_m (WD_2), a proposed correction for unknown B_m (WD_3), the TBW estimated from body composition (WD_4), the actual plasma sodium (WD_5), the substitution of plasma osmolality (Posm) for sodium (WD_6), and actual Posm (WD_7).

Results: Dehydration reduced TBW by 3.49 ± 0.91 L, 57% of which (2.02 ± 0.96 L) was FW loss, and increased plasma sodium from 139 (range: 135–143 mmol/L) to 143 (range: 141–148 mmol/L) mmol/L. Calculations for WD_1 through WD_7 all underestimated TBW loss by 1.5–2.5 L ($P < 0.05$). WD_1 through WD_5 underestimated FW by 0.5 L to 1.0 L ($P < 0.05$), but WD_6 and WD_7 estimated FW loss to within 0.06–0.16 L ($P > 0.05$).

Conclusions: WD_1 grossly underestimates TBW and FW losses. Corrections for unknowns and assumptions (WD_2 through WD_5) improved estimates little. The use of $WD_6 = 0.6 \times B_m \times [1 - (290 \div Posm)]$ accurately estimates FW but still underestimates TBW losses by >40%. *Am J Clin Nutr* 2013;97:79–85.

INTRODUCTION

Hyperosmolar-hypovolemia (dehydration) is a significant clinical problem (1–7) seen in critically ill patients, frail populations, athletes, and military personnel participating in hot-weather activities (8, 9). When significant water deficits require replacement therapy (5), the initial replacement volume can be calculated from the water-deficit equation (WD_1)⁵ (10). After the initial fluid volume is administered, the subsequent therapeutic management decisions are based on serial monitoring of differential water and electrolyte fluxes (1, 5, 6). However, any error in the initial therapeutic replacement volume calculated from WD_1 may increase the duration and clinical effort required to normalize the hyperosmolar disorder of the patient.

WD_1 is a simplified osmotic prediction formula (10) that has been used to guide initial fluid-replacement therapy for >50 y. Although the generalized assumptions behind WD_1 were in-

tended for use where experimental precision is not possible (10), the potential errors associated with its application in treating hyperosmolar-hypovolemia have not been systematically evaluated. WD_1 is commonly applied in medicine and nutrition in the following form (3, 5, 7, 10–14):

$$0.6 \times B_m \times [1 - (140 \div Na^+)] \quad (1)$$

(where B_m denotes body mass) to estimate the volume (L) of water required to normalize the plasma sodium concentration and, thereby, correct dehydration. WD_1 estimates total body water (TBW) losses that are free of solute [free water (FW)]. One potential error in the calculation of FW losses is the difference between current (dehydrated) and typical (euhydrated or premorbid) B_m , the latter of which is usually unknown (3, 11, 13, 14). Equation assumptions related to body composition (usually 60% body water) and a normal plasma sodium set equal to the population median (140 mmol/L) are also potential contributors to estimation error (3, 13) because there is considerable individual variation in these assumptions. Because WD_1 estimates FW losses, it will also underestimate TBW losses by the simple fact that body fluids (sweat, urine, and gastrointestinal secretions) contain varying amounts of solute (1, 3, 5, 6, 13). Although it has been acknowledged that FW losses will underestimate TBW losses “to some extent” (1, 5), no study, to our knowledge, has systematically quantified the magnitude of error in FW or TBW estimates by using WD_1 .

The purpose of this study was to quantify the extent to which WD_1 accurately estimates FW and TBW losses in response to dehydration and include a systematic test of equation unknowns and assumptions. Knowledge of FW and TBW estima-

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⁵ Abbreviations used: B_m , body mass; FW, free water; OAS, osmotically active substance; Posm, plasma osmolality; SD_{diff} , SD of the difference; TBW, total body water; WD_1 , water-deficit equation.

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tion errors might allow improvements to the equation and, thereby, improve the management of patients with hyperosmolar disorders.

SUBJECTS AND METHODS

Subjects

Thirty-six healthy and physically fit soldier volunteers (30 men and 6 women) were recruited for the study beginning in June 2007. The use of alcohol, dietary supplements, and any medication other than an oral contraceptive was prohibited. Volunteers were provided informational briefings and gave voluntary, informed written consent to participate. Investigators adhered to Army Regulation 70–25 and US Army Medical Research and Materiel Command Regulation 70–25 on the use of volunteers in research. The study was approved by the US Army Research Institute of Environmental Medicine Human Use Review Committee.

Experimental design

One day before testing, volunteers were given 3.0 L fluid to consume in addition to ad libitum beverage consumption and habitual dietary practices. Volunteers were instructed to consume a premeasured volume of water (1.0 L) between waking and 1800 and an additional volume of sports drink (2.0 L) between 1800 and 2200. It was estimated that food intake would provide an additional 0.6 L fluid each day (8), which would bring daily fluid intake totals to ≥ 3.6 L (8). Physical exercise was permitted but was restricted to a short list of allowable activities and work durations. No food or drink was permitted between 2230 and 0630 the next morning (an 8-h fast).

On the test day, volunteers awoke, voided a first-morning urine sample at the laboratory at 0630, and, immediately after, their nude B_m was measured. Blood was drawn after 30 min in a seated posture with a controlled arm position. A small, standardized breakfast (0.25 L H_2O , 550 kcal) and 30-min rest period followed. Volunteers entered an environmental chamber set to an air temperature of 40–50°C and ~20% relative humidity. Volunteers performed intermittent treadmill walking to induce dehydration via a combination of sweating and fluid restriction. Exercise duration was varied intentionally from 3 to 5 h in subjects to produce a range of TBW losses. A 90-min break followed the exercise-heat exposure, whereby volunteers showered and rested. After the break, nude B_m was again measured for comparison with preexercise values, and a second blood sample was drawn after ≥ 30 min in a seated posture.

Analytic measures and calculations

Anthropometric measures

Nude B_m (kg) was measured by using a platform scale (Model WSI-600; Mettler Toledo) that was accurate to ± 0.05 kg. Body density was determined via the sex-specific 3-site skinfold-thickness method by using Lange Skinfold Calipers (Beta Technology Inc) (15). Body composition was calculated from body density using the appropriate population-specific formulas (15). Lean B_m and fat mass were determined by the simple

product of B_m and the percentage of body fat. The 2-compartment Siri model of body composition, although simple, provides excellent agreement with more sophisticated techniques for estimating the hydration fraction of lean and adipose tissue under euhydrated conditions (16).

Blood and urine

The first-morning urine sample was voided into a sterile, inert polypropylene cup (Tyco Health care Group) and analyzed for specific gravity by using a refractometer (1110400A TS Meter; AO Reichert Scientific Instruments). A 3-mL sample of venous blood was collected without stasis in lithium-heparin tubes (Sarstedt Inc). Blood samples were centrifuged ($1250 \times g$) at 5°C for 15 min, and plasma was separated for analysis without delay (17). Plasma osmolality (Posm) was measured by a single technician by using freezing-point depression with an osmometer (Fiske Micro-osmometer, Model 210; Advanced Instruments Inc) that was calibrated by using standards in the 290-mmol/kg reference range. Samples were run in triplicate, and the median value taken as final. If any of the intrasample triplicate measures differed by $> 1.0\%$, the median of 5 samples was used. This approach is recommended on the basis of the ordinate scale of the readings (17), and the desired imprecision was based on instrument resolution and the potential physiologic importance of small fluctuations ($\geq 1.0\%$) in Posm to hormonal fluid regulation (18). A similar procedure was used for plasma sodium, which was measured by using a PolyChem analyzer (Polymedco). The mean intrasample CV for Posm was 0.58%. Two-thirds of samples were completed in triplicate, and one-third of samples required 5 samples by using the previously stated methodology. All plasma sodium samples were completed by using triplicate measures with a mean intrasample CV of 0.50%.

Calculations

TBW was calculated as $0.724 \times \text{lean } B_m + 0.255$ (19). In response to acute exercise-heat exposure, water (sweat and urine) volume and B_m losses were considered equivalent (1 L = 1 kg) (20, 21) after correction for carbon exchange, which was estimated at ~ 1 g/min during heat exposure (22). The level of dehydration was calculated from the corrected change in nude B_m between 0630 and 90-min postexercise and was expressed as a percentage of starting (euhydrated or premorbid) B_m in accordance with

$$(\Delta B_m \div B_m) \times 100 \quad (2)$$

Percentage changes in TBW were calculated similarly. FW losses and total losses of osmotically active substances (OASs) were calculated from TBW losses and Posm by using the algebraic rearrangement of equations detailed by Nose et al (23). Briefly, the FW-loss concept is analogous to FW clearance used to evaluate renal function. In this model, FW losses are zero when the concentration of OAS loss is isotonic with plasma. Because sweat is approximately one-half the tonicity of plasma, sweating should produce FW losses that approximate 50% of TBW losses (23, 24). A more-precise estimate of FW losses can be obtained by solving for x in the equation

$$\Delta \text{Posm} = (\text{Posm}^0 \div \text{TBW}^0) \times x \quad (3)$$

where ΔPosm is the change in Posm that occurs with dehydration, and Posm^0 and TBW^0 represent euhydrated

Posm and TBW, respectively (23). Solving for x in the equation

$$P'_{\text{osm}} = [\text{Posm}^0 \times \text{TW}^0 - (\Delta\text{TW} \times x)] \div \text{TW}^0 - \Delta\text{TW} \quad (4)$$

provides the total loss of OASs, where P'_{osm} is Posm when dehydrated, and ΔTBW is the change in TBW that occurs with dehydration. For additional details, see Nose et al (23).

WD_1 was calculated (Equation 1) to estimate the volume of FW required to correct dehydration (3, 5, 7, 10–14). Assumptions within the equation were tested by systematically substituting measured values for estimated values. A summary of the substitutions applied is shown in **Table 1**. The equations included substitution of the known euhydrated B_m (WD_2), substitution of a correction (14) for the unknown euhydrated B_m (WD_3), substitution of the TBW (rather than 60%) estimated from the measured body composition (WD_4), and substitution of the actual euhydrated plasma sodium (WD_5) for the 140 mmol/L standard. A substitution of Posm of 290 mmol/kg for plasma sodium of 140 mmol/L was evaluated (WD_6) on the basis that a typical euhydrated Posm is taken to be ≤ 290 mmol/kg (9), which is also well within the typical reporting range of 285–295 mmol/kg (3, 17, 25–27). Finally, the universal potential for the use of WD_6 was evaluated by substituting the actual Posm (WD_7) for plasma sodium 140 mmol/L.

Statistical analysis

All data were analyzed by using parametric statistics after the omnibus D'Agostino test for normality. Single-measurement comparisons in groups were made by using 1-factor repeated-measures ANOVA. Tukey's post-hoc procedure was used when a significant main effect was shown. Simple euhydration compared with dehydration trial comparisons were made by using a paired t test. Ordinary least-squares regression was also performed to compare the slopes and intercepts of select data sets. All data were analyzed with GraphPad Prism 5.0 software (GraphPad Software Inc) and are presented as means $\pm$ SDs unless otherwise indicated.

A primary purpose of this study was to quantify the extent to which WD_1 accurately estimates TBW and FW losses in response to dehydration. The SD of the difference between measurements (SD_{diff}) was used to estimate ($\text{SD}_{\text{diff}} \div \sqrt{2}$) that the level of uncertainty in measured TBW losses would be ~ 0.50 L on the basis of a diurnal intrasubject SD_{diff} value

for B_m between 0.45 and 0.85 kg (ie, 0.5–1.0% of 85 kg) (27, 28), where (20, 21)

$$\Delta\text{TBW (L)} = \Delta B_m(\text{kg}) \quad (5)$$

This value was also similar to the volume error associated with use of Equation 3 for the calculation of FW losses (23) when applying ± 2 mmol/kg for ΔPosm measurement imprecision (27). It was estimated that <10 subjects would be required to detect a difference >0.50 L when common statistical assumptions ($\alpha = 0.05$, $\beta = 0.20$; $\rho \geq 0.5$; effect size >1.0) were used for repeated-measures ANOVA (29). Therefore, to better interpret the presence or absence of statistical significance, the practical importance of the effect magnitude was estimated by plotting the 95% confidence limits for the mean difference (measured compared with estimated) in FW losses. This is a corollary for significance testing (30, 31) that provides insight into the likely range of true population differences. In addition, 95% confidence limits were evaluated against an a priori indifference zone or trivial effect, which is similar to equivalence testing (31, 32). The importance of mean volume differences was considered marginal, independent of the P value, if they were smaller than the level of measurement uncertainty (ie, 0.50 L) (32). Wynn (10) similarly considered volume measurement errors <0.50 L of no clinical importance.

RESULTS

Verbal compliance with fluid intake and a first morning urine specific gravity < 1.02 was considered confirmatory of a euhydrated state in all volunteers on their arrival to the laboratory (9). Anthropometric and TBW descriptive data of subjects are provided in **Table 2**. The 36 volunteers tested varied considerably in B_m , body fat, TBW, and percentage of TBW, which provided a valid range from which 2 key equation assumptions (B_m and composition) could be tested. The level of dehydration achieved is shown in **Table 3**. Dehydration reduced TBW by 3.49 ± 0.91 L, which ranged from mild (2.2%) to severe (5.8%), which allowed a meaningful context for any applications. TBW loss was hypotonic as indicated by calculated OAS losses (42 ± 24 mmol/L).

Mean TBW- and FW-volume losses are plotted in **Figure 1**. FW losses (2.02 ± 0.96 L) represented 57% of TBW losses. FW deficits estimated by using WD_1 through WD_7 all grossly underestimated TBW loss by 1.5–2.5 L ($P < 0.05$). FW losses estimated by WD_1 through WD_5 also significantly underestimated FW by 0.5 to 1.0 L ($P < 0.05$). As shown in **Figure 2** for WD_1 through WD_5 , mean differences and more than one-half of the 95% CI for mean differences fell outside the indifference zone or zone of measurement uncertainty (± 0.50 L). Thus, significant differences observed for WD_1 through WD_5 were also considered meaningful because they fell outside the indifference zone. In contrast, WD_6 and WD_7 accurately estimated FW loss to within 0.06–0.16 L ($P > 0.05$). Mean differences for WD_6 and WD_7 were very similar, and their 95% CIs fell entirely within the indifference zone, which indicated that the differences were inconsequential and could be effectively ignored (ie, equivalent) (32). The noticeably smaller CI width in WD_7 (Figure 2) was secondary to the algebraic equivalence of

TABLE 1

Water-deficit equation and derivatives for testing errors of assumption¹

WD_1	$0.6 \times B_m \times [1 - (140 \div \text{Na}^+)]$
WD_2	$0.6 \times B_{mX} \times [1 - (140 \div \text{Na}^+)]$
WD_3	$\{0.6 \times B_m \times [1 - (140 \div \text{Na}^+)]\} \div \{1 - 0.6 \times [1 - (140 \div \text{Na}^+)]\}^2$
WD_4	$0.X \times B_m \times [1 - (140 \div \text{Na}^+)]$
WD_5	$0.6 \times B_m \times [1 - (\text{Na}^+_X \div \text{Na}^+)]$
WD_6	$0.6 \times B_m \times [1 - (290 \div \text{Posm})]$
WD_7	$0.6 \times B_m \times [1 - (\text{Posm}_X \div \text{Posm})]$

¹ B_m , body mass; Posm, plasma osmolality; X, measured value; WD, water-deficit equation.

² Adapted from reference 14.

TABLE 2
Volunteer descriptive data (*n* = 36; 30 men and 6 women)

	Mean ± SD	Range
Age (y)	23 ± 4	18–32
Height (cm)	180 ± 10	160–190
Mass (kg)	84.8 ± 13.0	65.9–110.7
Percentage of body fat	18.2 ± 6.7	8.2–33.8
Total body water (L)	50.9 ± 8.7	33.4–64.0
Total body water (%) ¹	60 ± 1	48–67

¹ Percentage of body mass.

FW and WD₇ equations and synonymous Posm measures in both. The fact that WD₇ remained an imperfect estimator of FW losses, despite the use of identical Posm values in each formula, was precisely accounted for by differences in estimated TBW between FW and WD₇ (ie, ΔB_m). TBW was estimated by using euhydrated TBW (ie, TBW⁰) in FW and by using dehydrated TBW (postmorbidity) in WD₇ (see Subjects and Methods), and thus, WD₇ – FW was subtly (–0.16 L) but uniformly (36 of 36 observations) negative (Figure 2).

Individual subject plasma sodium and Posm when euhydrated and dehydrated are shown in **Figure 3**. For plasma sodium, 27 of 36 euhydrated values were <140 mmol/L, and only 1 of 36 euhydrated values met the criteria for clinical hypernatremia after dehydration (≥ 145 mmol/L) (1, 5, 32). For Posm, 35 of 36 euhydrated values were <301 ± 5 mmol/kg by ≥1 SD (≤296 mmol/kg), whereas 31 of 36 values were above the same threshold (≥ 296 mmol/kg) when dehydrated (26). Significant mean increases in plasma sodium and Posm were observed in response to consistent (36 of 36) directional changes among subjects. The mean increase in plasma sodium concentrations was 4 ± 1 mmol/L, and the mean increase in Posm concentrations was 11 ± 5 mmol/kg. Individual changes in Posm and plasma sodium concentrations (*y* axis) plotted as a function of the level of dehydration (*x* axis) are shown in **Figure 4**. A significant difference (*P* < 0.05) was observed between the slopes of the regression lines for Posm and plasma sodium, whereby Posm increases at a faster rate than plasma sodium in conjunction with increasing dehydration severity.

DISCUSSION

To our knowledge, this was the first study to systematically evaluate the water-deficit equation. We showed a large magnitude of error in WD₁ when applied to estimate TBW and FW losses after experimental dehydration. We also systematically tested

TABLE 3
Losses of body water and solute (*n* = 36; 30 men and 6 women)

	Mean ± SD	Range
Body mass loss (%) ¹	4.0 ± 0.8	2.2–5.8
Total body water loss (%) ²	6.6 ± 1.3	4.5–9.8
Free water loss (%) ³	57.0 ± 22.0	13.9–94.0
OAS ⁴ loss (mmol/L)	42 ± 24	10–122

¹ Percentage of body mass.

² Percentage of total body water.

³ Percentage of total body water loss.

⁴ OAS, osmotically active substance.

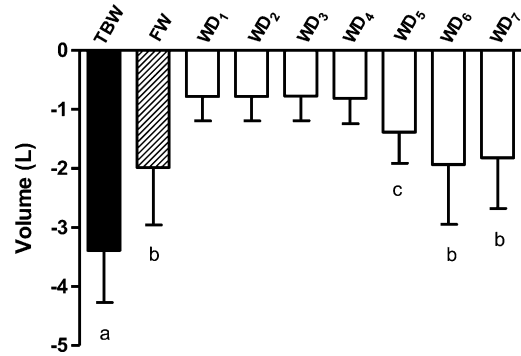


FIGURE 1. Measured changes in TBW, FW, and estimated FW losses using WD₁ through WD₇. a > all; b > WD₁ through WD₅; c > WD₁ through WD₄. Values > were significantly different (repeated-measures ANOVA) at *P* < 0.05 (*n* = 36 per group). FW, free water; TBW, total body water; WD, water-deficit equation.

common equation assumptions and determined that their correction was unnecessary. We showed that FW-loss estimates were most accurate when Posm was substituted for plasma sodium in the form

$$0.6 \times B_m \times [1 - (290 \div \text{Posm})] \quad (6)$$

We also concluded that Posm 290 is a reasonable standard substitution because of the small differences between WD₆ and WD₇ (*P* > 0.05). Strengths of this study included the use of a broad and clinically relevant range of moderate-to-severe dehydration (achieved prospectively by using careful weight-based methods to include metabolic corrections) and the use of a large number of subjects with a broad range of B_m and composition.

Fluid-replacement estimates by using WD₁ (~1 L) grossly underestimated TBW loss (~3.5 L) by 2.5 L. Because WD₁ provides an estimate of FW losses, it was expected to underestimate TBW losses because sweat, urine, or gastric secretions contain solute (1, 3, 5, 6, 13). We used sweat loss to reduce TBW by ~3.5 L, 57% of which (~2 L) was calculated as FW loss. The calculated loss of OASs ranged from 10 to 122 mmol/L with a mean of 42 mmol/L (Table 3), which were entirely consistent with values reported for direct measurements of sweat (23, 24). Therefore, WD₁ will underestimate TBW losses incurred from sweating by >70% (Figure 1).

We also showed, for the first time to our knowledge, that WD₁ markedly underestimates FW losses by 50% (~1.0 L) (Figures 1 and 2). Nearly identical results were observed for WD₂ through WD₄ (Figures 1 and 2). The average correction for dehydrated B_m was 3.5 kg, whereas body water ranged from 48% to 67% of B_m (Figure 1; Table 2). These observations suggest that neither the knowledge of the euhydrated (pre-morbidity) B_m nor correction for the 60% body-water assumption provides any benefit for the reduction of the WD₁ estimation error. This finding negates concerns over an unknown premorbidity B_m (3, 11, 13, 14) as well as the potential need to adjust the equation for the percentage of body water (~50–70%) on the basis of sex or age (1, 5, 33–35). Although the small number of women (*n* = 6) and the modest age range (18–32 y of age) in this study did not allow explicit sex- or age-based comparisons, the large potential differences in body composition because of sex or age were addressed in WD₄ by the wide ranges in the

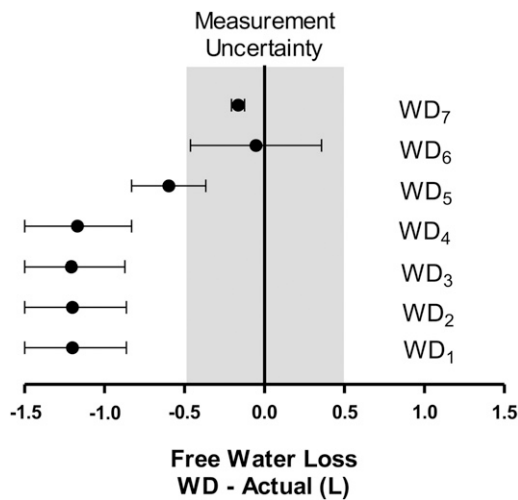


FIGURE 2. Mean differences ($\pm 95\%$ CIs) ($n = 36$ per group) of FW estimation errors for WD₁ through WD₆. The shaded band (measurement uncertainty) was calculated as $SD_{\text{diff}} \div \sqrt{2}$ for repeat (day-to-day) measures of euhydrated nude body mass. Mean differences outside the shaded band were considered meaningful. FW, free water; SD_{diff} , SD of differences; WD, water-deficit equation.

percentage of body fat (8.2–33.8%), percentage of body water (48–67%), and body-water volume (33.4–64 L) that were studied. The substitution of the measured euhydrated plasma sodium for the constant 140 mmol/L within the equation numerator of WD₅ significantly ($P < 0.05$) reduced the FW loss error because 27 of 36 euhydrated plasma sodium values were < 140 mmol/L. The insertion of any plasma sodium value less than 140 mmol/L into the WD₁ equation numerator increased the FW volume estimate, but the error remained larger than the ± 0.50 L zone of measurement uncertainty (Figure 2).

The substitution of Posm for plasma sodium in WD₆ (Equation 6) provided the most accurate estimates of FW losses (0.06 L; $P > 0.05$) (Figures 1 and 2), although it still underestimated TBW losses by 43% (Figure 1). A potential bias of this substitution relates to the use of Posm for calculating FW losses (23). Although direct measures of OASs in sweat, urine, or gastric secretions would be the gold standard for this purpose, the volume of TBW losses in this study were almost entirely derived from sweat and were corrected for metabolic exchange (22) in accordance with standard laboratory procedures (27). Unlike urine, which contains a large portion of osmotically permeable urea that can underestimate FW losses (36), sweat contains very little urea (24). As a result, sweat losses provide an FW-loss estimate that is akin to the more-accurate calculation of electrolyte-free renal water loss (36, 37). Therefore, the loss of OASs from sweat can be reasonably calculated, with little bias, from basic algebraic equations (23) when Δ TBW and Δ Posm are measured precisely. The application of WD₁ to situations in which dehydration occurs coincident with larger losses of solute (diarrhea, vomiting, and urine) would be clearly inappropriate and would logically underestimate FW losses to an even greater extent.

In our study, hypertonicity was not synonymous with hypernatremia. Instead, the clinical threshold for hypernatremia (≥ 145 mmol/L) (1, 5, 33) was reached by only 1 of 36 subjects despite carefully measured TBW deficits that averaged ~ 3.5 L (2.2–5.8% dehydration) (Figure 1; Table 3). In contrast, the observed

Posm value of 301 ± 6 mmol/kg (Figure 2) was remarkably consistent with the dehydration threshold value of 301 ± 5 mmol/kg proposed from an entirely independent data set (27). The observed change in Posm (11 ± 5 mmol/kg) was also consistent with a 95% probability of dehydration (38). Although both plasma sodium and Posm increased consistently in response to dehydration (Figure 3), their responses were a disproportional function of the level of dehydration, whereby the contribution of plasma sodium to Posm was reduced as the level of dehydration increased (Figure 4). This observation is intuitive and consistent with other reports (39), including an analysis presented by the Institute of Medicine (8) that showed a greater

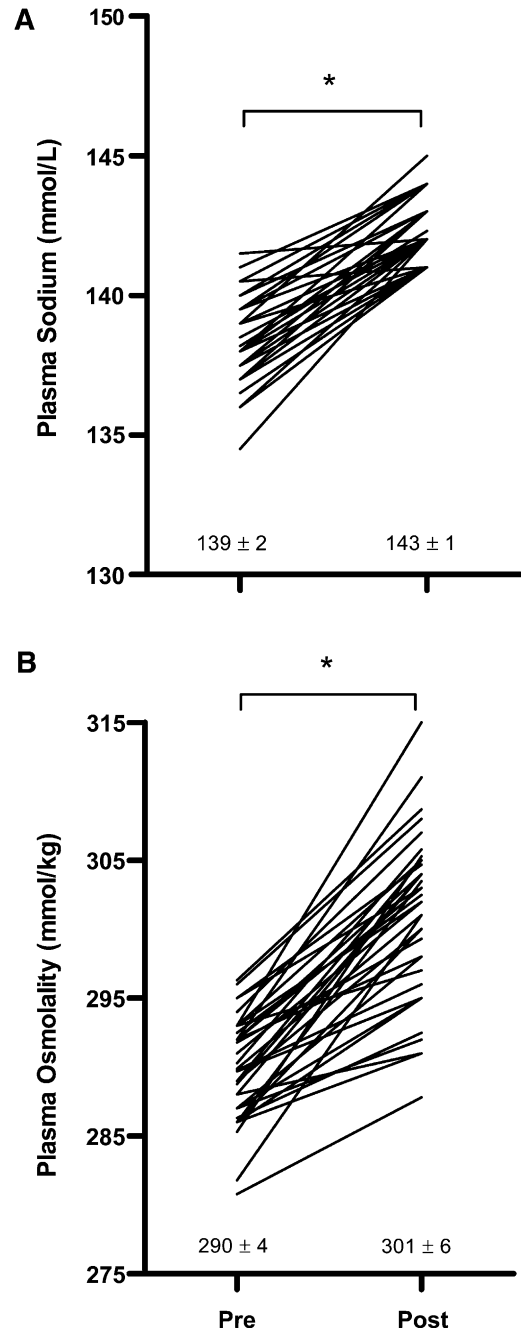


FIGURE 3. Individual and mean plasma sodium (A) and osmolality (B) measures. $*P < 0.05$ between euhydrated (Pre) and dehydrated (Post) conditions (paired t test; $n = 36$ pairs each).

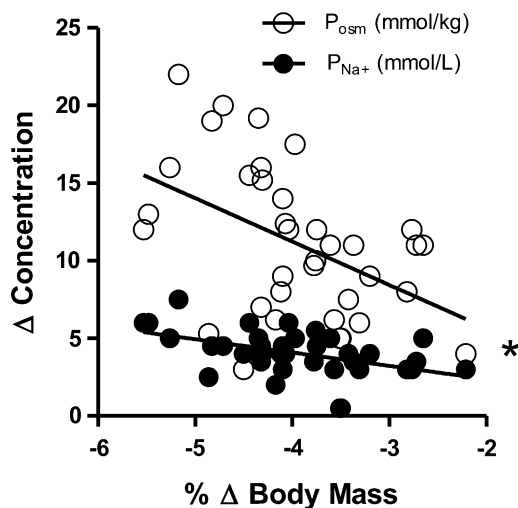


FIGURE 4. P_{osc} and P_{Na^+} concentrations (y axis) plotted as a function of the level of dehydration (x axis). *Slopes were significantly different, $P < 0.05$ ($n = 36$ observations for each variable). P_{Na^+} , plasma sodium; P_{osc} , plasma osmolality.

increase in Posm than plasma sodium with sweat-induced dehydration. A plausible explanation for this is that sodium is lost in sweat in amounts much larger than other substances (24) that contribute to Posm (cations, anions, proteins, and nonionized organic substances) (2, 40, 41), and thus, Posm increases as water is lost despite progressive sweat-sodium losses in the ordinary physiologic range (24). Tissue sodium retention somewhere within the extracellular matrix is another plausible contributor to this phenomenon, but unequivocal experimental evidence for this effect (42) has required conditions and protracted time frames very different from those in this study. Criticisms for the use of Posm instead of effective osmolality (tonicity) (35) are warranted when pathological glucose, urea, or unidentified osmoles (eg, ethanol) are concerned, but proper awareness of this potential (10, 33) can rule out a falsely elevated Posm by the direct measurement of osmotically active moieties such as sodium, glucose, and urea when a potential osmole gap is calculated (43). Therefore, the direct measure of Posm was considered synonymous with total plasma tonicity in this study of healthy volunteers and was supported by the fact that Posm rose disproportionately to plasma sodium in response to a simple intervention that involved only large volume losses of hypotonic sweat.

In conclusion, to our knowledge, our study is the first to systematically evaluate the frequently used WD_1 . Our findings support the use of Posm to improve estimation of FW losses for replacement regimens during initial stages of fluid therapy for hyperosmolar states, particularly when heavy sweating is the suspected etiology. Although the substitution of Posm for plasma sodium within WD_1 is not a new concept (35, 44), the value used for Posm has varied and, to our knowledge, was never validated as a substitute for plasma sodium. The current study provides empirical support for the use of a value of 290 mmol/kg. We also provide evidence that errors associated with an unknown premorbid B_m or the common assumption of 60% body water make little difference to estimation errors. As a result, WD_1 can remain a guide to initial fluid-replacement therapy in the modified form shown in Equation 6. This equation

provides a more accurate estimate of FW losses than does plasma sodium in response to hypotonic TBW losses but will still underestimate TBW losses by $>40\%$. These findings can be used to help inform and guide the acute management of hyperosmolar states (5).

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The authors' responsibilities were as follows—SNC, RWK, KJS, and BRE: data analysis; and all authors contributed to the study conception and design, data acquisition, analysis and interpretation of data, and writing and editing of the manuscript. None of the authors had a conflict of interest.

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