Serum Sodium Concentration and Tonicity in Hyperglycemic Crises: Major Influences and Treatment Implications

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Maintenance of the volume of all cells, particularly those of the central nervous system, is critical for their function and survival.[1–6] Tonicity (ie, effective osmolarity) of a solution refers to its property to cause osmotic fluid shifts into or out of cells suspended in it. Direct determination of serum tonicity is not readily available for clinical applications.[6] Serum sodium concentration ($[Na]_S$) is the main parameter used as a surrogate value for serum tonicity.[5–7] The only direct information provided by $[Na]_S$ is whether serum tonicity is normal (the volume of cells exposed to a serum with normal $[Na]_S$ is not affected), low (the volume of cells exposed to a serum with low $[Na]_S$ increases by osmotic intracellular transfer of water), or high (the volume of cells exposed to a serum with high $[Na]_S$ decreases by osmotic transfer of water out of the cells).[6,7]

In a pivotal study, Edelman and coinvestigators identified total body sodium, total body potassium, and total body water as the universal determinants of $[Na]_S$ in patients with various states potentially associated with extracellular volume disturbances.[8] Abnormalities in $[Na]_S$ usually result from changes in the external balance of one of its 3 determinants or a combination thereof. The relations between $[Na]_S$ and total body sodium, total body potassium, and total body water have been expressed by various formulas. The original Edelman formula expresses sodium concentration in plasma water.[8] The Nguyen and Kurtz formula expresses sodium concentration in plasma, which is essentially equal to $[Na]_S$.[9] Nguyen and Kurtz developed their formula by multiplying the components of the Edelman formula by a correction coefficient equal to 0.93, which represents the normal plasma water fraction. The Rose formula, which represents a simplified version of the Edelman formula, expresses $[Na]_S$ as the fraction (total body sodium plus total body potassium) over total body water.[10] Formulas calculating the tonicity of replacement solutions for correction of dysnatremias applied in clinical practice[11–14] are based on the Rose formula, which will also be the basis of the calculations in this review.

The principle that underlies the distribution of body water in the 2 major body-fluid compartments states that the intracellular/extracellular volume ratio is equal to the intracellular/extracellular solute ratio.[15] This relationship is a direct consequence of Peter's osmotic principle, which states that in the steady state, solute concentration (osmolality) is equal in the intracellular and extracellular fluids.[16] Total body sodium and potassium represent the major solutes in body fluids: sodium is essentially restricted in the extracellular compartment and potassium in the intracellular compartment. Consequently, total body sodium is a measure of effective extracellular solutes, whereas total body potassium represents the effective intracellular solutes.

Hyperglycemic crises create complex disturbances in body water and its distribution between the intracellular and extracellular compartments, in addition to tonicity problems not reflected directly in $[Na]_S$. This review analyzes the pathogenesis and treatment of hyperglycemic hypertonicity.

Serum Hypertonicity as an Exclusive Consequence of Development of Hyperglycemia

When solutes with extracellular distribution, other than sodium salts, do not exceed their normal concentration, the expression $2\times[Na]_S$ represents approximately 98% of serum

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tonicity. Solutes distributed in total body water, such as urea, ethanol, methanol, or propyl alcohol, increase osmolality but do not change this relationship between $[Na]_S$ and tonicity because they do not affect the volume of cells. In contrast, gain of solutes restricted in the extracellular compartment, other than sodium salts, causes hypertonicity resulting in osmotic fluid exit from the intracellular compartment and decrease in $[Na]_S$. In this case, $[Na]_S$ alone does not indicate the state of tonicity. Hypertonicity may result from gain of exogenous solutes with extracellular distribution, for example, mannitol or low-molecular-weight radiographic contrast agents. However, hyperglycemia is the major clinical condition that creates hypertonicity challenges from gain of extracellular solutes other than sodium salts.[17]

Glucose infused as a bolus is distributed in the extracellular compartment.[18–20] After glucose enters the cells, it is metabolized to carbon dioxide and water or compounds with negligible osmotic activity (eg, glycogen). Consequently, regarding internal solute balance, glucose is considered an extracellular solute that contributes to the tonicity of body fluids.[5–7 21,22] Gains in glucose raise the effective extracellular solute and result in hypertonicity.[21] Serum tonicity in patients with hyperglycemia is calculated as the sum of $2\times[Na]_S$ plus the serum glucose concentration ($[Glu]_S$) in mmol/L.[21]

Correction of hypertonicity constitutes one of the main aims and challenges of managing hyperglycemic crises.[22] Correction of hyperglycemia results in loss of effective extracellular solute[23] and osmotic transfer of extracellular water into the cells, leading to a rise in $[Na]_S$.[24] Serum tonicity decreases during correction of hyperglycemia because the decrease in osmolarity secondary to the decrease in $[Glu]_S$ ($\Delta[Glu]_S$) is greater than the corresponding increase in osmolarity secondary to the rise in $[Na]_S$ ($\Delta[Na]_S$).[24] The magnitude of the change in tonicity due to the level of correction of hyperglycemia must be accurately predicted because hyperglycemia causes a second major increase in body fluid tonicity through osmotic diuresis that requires additional measures for its correction.[7] This second hyperglycemic influence on tonicity will be addressed later in this report.

Table 1 shows formulas expressing the changes in the determinants of tonicity during development or correction of hyperglycemia in patients without changes in the external balances of water, sodium, or potassium (ie, in a closed system). The prediction of the extent of decrement in tonicity consequent to a given $\Delta[Glu]_S$ requires calculation of the $\Delta[Na]_S$ in addition to the projected $\Delta[Glu]_S$. A key step for this prediction was provided by Katz, who calculated that $[Na]_S$ decreases by 1.6 mmol/L for each increase in $[Glu]_S$ by 5.6 mmol/L, or by 100 mg/dL (formula 1 in Table 1).[25] In the same table, formula 2 by Al-Kudsi and collaborators, based on the Katz value of $\Delta[Na]_S/\Delta[Glu]_S$, predicts the value of $[Na]_S$ after a decrease of $[Glu]_S$ from any hyperglycemic level to 5.6 mmol/L.[26] The performance of the Al-Kudsi formula depends on the accuracy of Katz's predicted value of $\Delta[Na]_S/\Delta[Glu]_S$.

Studies of Katz's $\Delta[Na]_S/\Delta[Glu]_S$ Formula

The Katz formula has been subjected to theoretical analysis and clinical utility and reliability studies in a closed system and to clinical observations in an open system.

Closed-System Observations

Katz calculated the ratio $\Delta[Na]_S/\Delta[Glu]_S$ assuming only an increase in extracellular glucose content and no external changes in body water or monovalent cations (ie, in a closed system). Several theoretical analyses that elaborated on and extended Katz's calculations identified the mathematical determinants of $\Delta[Na]_S/\Delta[Glu]_S$ in a closed system.[27–32] The glucose gained per liter of the baseline extracellular volume ($[Glu]_A$) and the ratio of intracellular/extracellular volume at baseline euglycemia (ratio α_1) were shown to be the dominant determinants of the magnitude of the changes induced by development of hyperglycemia in a closed system, including internal osmotic volume shifts, changes in tonicity, $[Na]_S$ and $[Glu]_S$, and the ratio $\Delta[Na]_S/\Delta[Glu]_S$.[30,31] The contribution of $[Glu]_A$ to the magnitude of osmotic fluid shifts and changes in tonicity, $[Na]_S$, and $[Glu]_S$ is intuitive. Its contribution to the $\Delta[Na]_S/\Delta[Glu]_S$ ratio will be discussed below.

The ratio of intracellular/extracellular volume (ratio α) decreases during expansion of the extracellular volume due to either salt and water retention or osmotic transfer of intracellular water into the extracellular compartment in states of hypertonicity, and it increases during development of hypovolemia from external fluid losses or from transfer of extracellular water into the cells in states of hypotonicity. The contribution of the euglycemic volume ratio to the changes in tonicity, $[Na]_S$, and $[Glu]_S$ induced by hyperglycemia is a consequence of the fact that total body water determines the change in tonicity secondary to gain in solute with extracellular distribution along with the amount of solute gained.[5] The increase in serum tonicity (ΔTon) after a gain in $[Glu]_S$ is expressed as the algebraic sum $\Delta[Na]_S+\Delta[Glu]_S$. Note that $\Delta[Na]_S$ has a negative sign because $[Na]_S$ decreases during development of hyperglycemia.[24] ΔTon is determined by the amount of glucose gained divided by total body water, whereas $\Delta[Glu]_S$ is equal to the amount of glucose gained divided by extracellular volume.[5] Therefore, the relationship between extracellular volume and total body water is a major determinant of the ratios $\Delta Ton/\Delta[Glu]_S$ and $\Delta[Na]_S/\Delta[Glu]_S$.[29–31] The baseline volume ratio (α_1) is the most

Table 1. Formulas Expressing Serum Tonicity and Its Indexes in a Closed System of Hyperglycemia

Katz formula for $\Delta[Na]_S/\Delta[Glu]_S$ $\left(\frac{\Delta[Na]_S}{\Delta[Glu]_S}1\right)$[25]: $$\frac{\Delta[Na]_S}{\Delta[Glu]_S}1 = -1.6\frac{mmol}{L}\text{ per }5.6\frac{mmol}{L} \quad (1)$$
$[Na]_S$ at hyperglycemia corrected to $[Glu]_S$ of 5.6 mmol/L using the Al-Kudsi formula[26]: $$[Na]_{SCorrected1} = [Na]_{S2} + 1.6 \times \frac{[Glu]_{S2} - 5.6}{5.6} \quad (2)$$
Complete $\Delta[Na]_S/\Delta[Glu]_S$ formula expressing development of hyperglycemia in a closed system $\left(\frac{\Delta[Na]_S}{\Delta[Glu]_S}2\right)$[30]: $$\frac{\Delta[Na]_S}{\Delta[Glu]_S}2 = -\frac{\alpha_1 \times [Na]_{S1}}{(\alpha_1+1)\times 2\times [Na]_{S1} + [Glu]_{S1} + [Glu]_{A1}} \quad (3)$$
$[Na]_S$ in hyperglycemia corrected to any given euglycemic value in a closed system using formula 3: $$[Na]_{SCorrected2} = [Na]_{S2} + \Delta[Glu]_{S2} \times \frac{\alpha_2 \times [Na]_{S2}}{(\alpha_2+1)\times 2\times [Na]_{S2} + [Glu]_{S2} + [Glu]_{A2}} \quad (4)$$
The value $\Delta[Glu]_S$ as a function of $[Glu]_A$ during development of hyperglycemia[30]: $$\Delta[Glu]_S = [Glu]_{A1} \times \frac{(\alpha_1+1)\times 2\times [Na]_{S1} + [Glu]_{S1} + [Glu]_{A1}}{(\alpha_1+1)\times(2\times [Na]_{S1} + [Glu]_{S1} + Glu_{A1})} \quad (5)$$

$[Glu]_S$, $\Delta[Glu]_S$, and $[Glu]_A$ are expressed in mmol/L in formulas 1 through 5; formula 3 expresses the ratio $\Delta[Na]_S/\Delta[Glu]_S$ in mmol/L per mmol/L. Comparison of its results to the results of formula 2 requires multiplication of its findings by 5.6; formula 2 with the original expression of $[Glu]_S$ in mg/dL[26] is as follows:

$$[Na]_{SCorrected1} = [Na]_{S2} + 1.6 \times \frac{[Glu]_{S2} - 100}{100}.$$

$[Glu]_{A2}$ has a negative value in formula 4; formula 4 requires prior calculation of $\Delta[Glu]_{S3}$ by formula 5. Subscript numbers indicate stage. α indicates intracellular/extracellular volume ratio; $\Delta[Glu]_S$, change in serum glucose concentration; $\Delta[Na]_S$, change in serum sodium concentration; $[Glu]_A$, change in glucose concentration per liter of baseline extracellular volume; $[Glu]_S$, serum glucose concentration; $[Na]_S$, serum sodium concentration; $[Na]_{SCorrected}$, corrected serum sodium concentration. The subscripts 1 and 2 refer to euglycemia and hyperglycemia, respectively.

appropriate expression of the relationship between extracellular volume and total body water.[30] For a given degree of hyperglycemia, the rise in tonicity will be lower, and thus the decrease in $[Na]_S$ will be greater, when the baseline intracellular volume is very large in comparison to the extracellular volume (ie, in a volume-depleted state in which the volume ratio α_1 has a large value), because the abundance of intracellular volume provides a relative abundance of water for osmotic exchanges. An abundance of extracellular volume in edematous states, characterized by low value of the ratio α_1, has effects exactly opposite those of a high value α_1 on the rise in tonicity and drop in $[Na]_S$ during development of hyperglycemia because the intracellular water available for osmotic exchanges is relatively sparse in this case.

Another determinant of changes induced by glucose gain in a closed system is the baseline tonicity, which is composed of the baseline $[Na]_S$ ($[Na]_{S1}$) and the baseline serum glucose concentration ($[Glu]_{S1}$).[30] In Table 1, formula 3 expresses the $\Delta[Na]_S/\Delta[Glu]_S$ value as a function of its identified determinants,[30] whereas formula 4 expresses the corrected sodium for the degree of hyperglycemia $[Na]_S$, which is calculated using the $\Delta[Na]_S/\Delta[Glu]_S$ expression in formula 3.

The degree of hyperglycemia characterizes, along with other clinical and laboratory features, the severity of hyperglycemic crises.[17,22] The amount of glucose that needs to be added to the extracellular fluids to produce similar degrees of hyperglycemia depends on the extracellular volume. The value $[Glu]_A$, which is the glucose added—or removed—per liter of initial extracellular volume, was introduced in formulas 3 and 4 because it allows comparable $\Delta[Glu]_S$ values in patients with varying extracellular volumes. The total amount of glucose gain is the product $[Glu]_A$ times the baseline extracellular volume. Note that although $[Glu]_A$ and $\Delta[Glu]_S$ express the same change in body glucose, the values differ because $[Glu]_A$ is a measure of the glucose gain or loss per liter of the baseline extracellular volume, whereas $\Delta[Glu]_S$ expresses the difference between $[Glu]_S$ values in 2 different states of extracellular volume: the baseline state and the state after the change in extracellular glucose content. In a closed system,

extracellular volume increases during development of hyperglycemia and decreases during its correction. The relationship between $[Glu]_A$ and $\Delta[Glu]_S$ is expressed by formula 5 in Table 1.[30] Figure 1 shows $[Glu]_S$ changes for widely varying values of the volume ratio α_1 and $[Glu]_A$.

Regardless of the status of extracellular volume, as $[Glu]_S$ rises, the value $\Delta[Glu]_S$ becomes progressively lower than the value $[Glu]_A$ because extracellular volume increases progressively as $[Glu]_S$ rises in a closed system. However, the same $[Glu]_A$ produces comparable $\Delta[Glu]_S$ values at different states of extracellular volume even in extreme hyperglycemia. For example, if baseline $[Na]_S$ and $[Glu]_S$ values are 140 and 5.6 mmol/L, respectively, and $[Glu]_A$ is 112 mmol/L (2016 mg/dL), $\Delta[Glu]_S$ by formula 5 will be 92.1 mmol/L (1659 mg/dL) in euvolemia (α_1=1.50), 87.2 mmol/L (1567 mg/dL) in severe hypovolemia (α_1=3.00), and 95.4 mmol/L (1717 mg/dL) in severe hypervolemia (α_1=1.00). Figure 2 shows the ratio $\Delta[Na]_S/\Delta[Glu]_S$ for widely varying values of the volume ratio α_1 and $[Glu]_A$.

The numerical values of the ratio $\Delta[Na]_S/\Delta[Glu]_S$ calculated by formula 3 (Table 1) decrease progressively at progressively lower values of the volume ratio α_1 (ie, at progressively higher gains in extracellular volume) [30] and at progressively higher values of $[Glu]_A$ (progressive degree of hyperglycemia).[28–31] The numerical values of the ratio $\Delta[Na]_S/\Delta[Glu]_S$ decrease progressively in progressive hyperglycemia because of the progressive decrease in the volume ratio α.[31] Values of the ratio $\Delta[Na]_S/\Delta[Glu]_S$ numerically <1.6 mmol/L per 5.6 mmol/L result in higher values of hyperglycemic $[Na]_S$ and serum tonicity than the values computed from the Katz formula.[25]

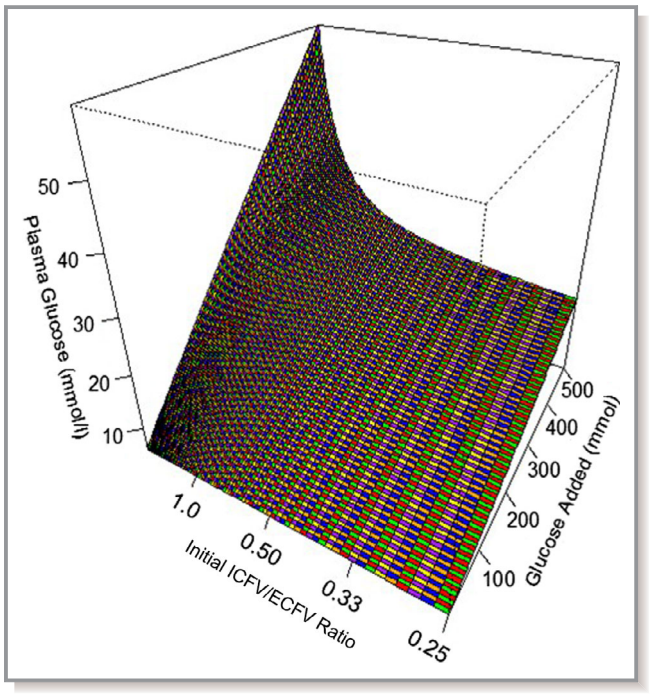

Figure 1. Plasma glucose concentrations at various levels of extracellular glucose gain and different ratios of euglycemic intracellular/extracellular volume (ICFV/ECFV ratio).

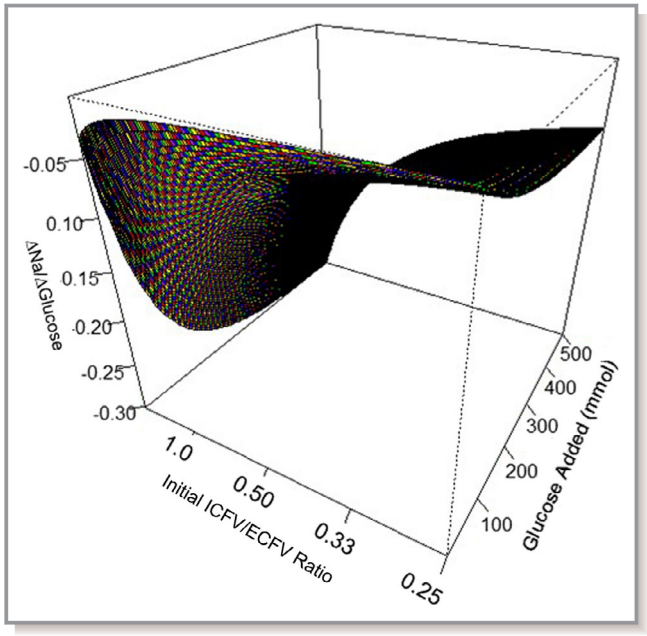

Figure 2. Change in serum concentrations of sodium over glucose ($\Delta[Na]_S/\Delta[Glu]_S$), in mmol/L per mmol/L, at different extracellular glucose gains and ratios of euglycemic intracellular/extracellular volume (ICFV/ECFV ratios) during development of hyperglycemia. $\Delta Na/\Delta Glucose$ indicates $\Delta[Na]_S/\Delta[Glu]_S$.

Figure 3 shows changes in $[Na]_S$ for widely varying values of the volume ratio α_1 and $[Glu]_A$. The values of hyperglycemic $[Na]_S$ computed by formula 4 differ substantially from the values computed by formula 2 (Table 1) in states of extreme extracellular volume excess or deficit. For example, if baseline $[Na]_S$ and $[Glu]_S$ values are 140 and 5.6 mmol/L, respectively, and $[Glu]_A$ is 112 mmol/L (2016 mg/dL), $[Na]_S$ at hyperglycemia will be 113.7 mmol/L by the Katz formula (formula 1 in Table 1) and 116.3 mmol/L by formula 4 (Table 1) in euvolemia (α_1=1.5), 115.1 mmol/L by formula 1 and 110.7 mmol/L by formula 4 in severe hypovolemia (α_1=3.0), and 112.8 mmol/L by formula 1 and 120.2 mmol/L by formula 4 in severe hypervolemia (α_1=1.0).

Finally, hyperglycemia causes potassium egress from cells because of lack of insulin, hypertonicity, and probably ketoacidosis.[33] Transfer of potassium from the intracellular into the extracellular compartment causes a decrease in total intracellular solute and an increase in total extracellular solute resulting in osmotic transfer of intracellular water into the extracellular compartment and a decrease in the volume ratio. A decrease in the numerical value of the $\Delta[Na]_S/\Delta[Glu]_S$ ratio will result from potassium exit from the cells.[29] Although clinically critical, potassium transfers have minimal effects on the ratio $\Delta[Na]_S/\Delta[Glu]_S$ and the internal osmotic fluid

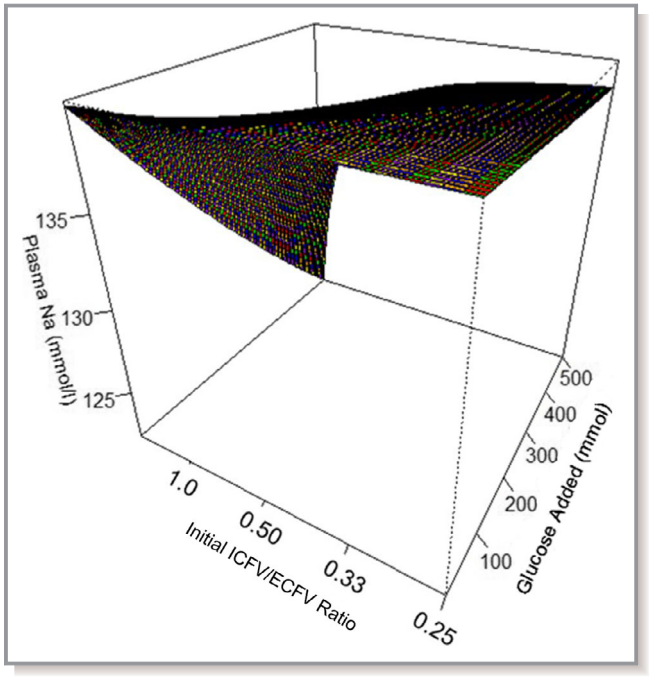

Figure 3. Plasma sodium concentrations at different extracellular glucose gains and different ratios of euglycemic intracellular/extracellular volume (ICFV/ECFV ratios).

shifts in oligoanuric patients because of the potentially lethal consequences of hyperkalemia from even a small potassium exit from cells in a closed system. The effect of potassium exit from the cells on the ratio $\Delta[Na]_S/\Delta[Glu]_S$ and the internal osmotic fluid shifts become significant in patients with preserved renal function and loss of potassium through osmotic diuresis. This last effect will be discussed below.

Hyperglycemia developing in oligoanuric patients offers the opportunity to study the closed-system predictions because it can be treated only with insulin infusion.[32] Studies of oligoanuric patients with severe hyperglycemia treated with insulin confirmed Katz's prediction overall.[24 34–36] Comparisons of $[Na]_S$ and $[Glu]_S$ values of patients on chronic dialysis at presentation with hyperglycemia with the corresponding values at euglycemia were also in broad agreement with Katz's predicted value of the ratio $\Delta[Na]_S/\Delta[Glu]_S$.[26,37–40]

Although the average computed $\Delta[Na]_S/\Delta[Glu]_S$ values were very close to Katz's predicted value in oligoanuric hyperglycemic patients treated with insulin, the range of computed individual $\Delta[Na]_S/\Delta[Glu]_S$ values was wide.[24,34,36] For example, in a study of 43 hyperglycemic episodes treated with insulin in patients on chronic dialysis with minimal water intake and minimal or absent urine output during treatment, the calculated $\Delta[Na]_S/\Delta[Glu]_S$ ratio as mean±SD was -1.50 ± 0.22 mmol/L per 5.6 mmol/L.[34] The variation in the values of the ratio $\Delta[Na]_S/\Delta[Glu]_S$ in this study was mainly attributed to variation in the volume ratio α_1. The numerical value of the ratio $\Delta[Na]_S/\Delta[Glu]_S$ was significantly lower in edematous compared with euvolemic oligoanuric patients.[34] This observation confirmed the theoretical calculations from formula 3 in Table 1. An effect of the degree of hyperglycemia on the $\Delta[Na]_S/\Delta[Glu]_S$ ratio was not found in these studies, probably because of the prediction that only extremely high $[Glu]_S$ values will produce values of the $\Delta[Na]_S/\Delta[Glu]_S$ ratio substantially lower numerically than the estimate from the Katz formula.[28,30,36]

Open-System Observations

Patients with preserved renal function represent an open system. The development of hyperglycemia in these patients is complicated by 2 processes not accounted for in Katz's formula: water intake secondary to thirst and osmotic diuresis.[6,22] The concept of water intake during development of hyperglycemia was supported by 3 studies that concluded hyperglycemia accounts for part of the interdialytic weight gain.[41–43] A fourth study disputed this finding.[44] However, the finding of hyponatremia in approximately a third of the patients on dialysis after correction of hyperglycemia with insulin infusion[34] provided strong support for the concept of water intake in this patient group. Osmotic diuresis exerts a major influence on body-fluid tonicity in hyperglycemic crises in patients with preserved renal function.[22] Retrospective observational[45–47] and prospective[48] studies that specifically assessed the validity of Katz's formula in patients with preserved renal function reported widely varying $\Delta[Na]_S/\Delta[Glu]_S$ ratio values. These variations were attributed to varying water intake and volume and composition of urine in patients with severe hyperglycemia.[6]

Katz's formula computes a rate of increase in tonicity during development of hyperglycemia ($\Delta Ton/\Delta[Glu]_S$) equal to 2.4 ($=5.6-2\times1.6$) mOsm/L per 5.6 mmol/L.[24] In a review article that analyzed tonicity issues in published reports of large numbers of severe hyperglycemic episodes, computed average $\Delta Ton/\Delta[Glu]_S$ ratio values (in mOsm/L per 5.6 mmol/L) were 1.9 in dialysis-associated hyperglycemia, 3.5 in diabetic ketoacidosis, and 8.1 in nonketotic hyperglycemic syndrome.[36] The average value of the $\Delta Ton/\Delta[Glu]_S$ ratio in patients on dialysis was slightly lower than the value predicted using Katz's formula, reflecting fluid intake and retention during development of hyperglycemia in this patient group. However, average $\Delta Ton/\Delta[Glu]_S$ values were 1.5-fold higher than Katz's value in episodes of diabetic ketoacidosis occurring in patients with preserved renal function and 3.4-fold higher than Katz's value in patients with preserved renal function who developed profound nonketotic hyperglycemia.[36] The source of the high $\Delta Ton/\Delta[Glu]_S$ ratio values in severe hyperglycemic episodes developing in patients with preserved renal function is the development of osmotic diuresis.[22]

Losses of water, sodium, and potassium through hyperglycemic osmotic diuresis can be profound. These losses can be indirectly estimated by computing the volume of water and the amounts of sodium and potassium retained from the replacement solutions during correction of hyperglycemic crises. For example, treatment of severe nonketotic hyperglycemia in the balance study of Arieff and Carroll resulted in average net gains of 9.1 L water, 407 mmol sodium, and 137 mmol potassium.[49] A characteristic feature of osmotic diuresis caused by various solutes other than sodium salts is that the sum of the urinary concentrations of monovalent cations (sodium plus potassium) is routinely lower than the normal $[Na]_S$.[50] Figure 4 shows average urinary sodium and potassium concentrations in patients with hyperglycemic osmotic diuresis reported in Arieff and Carroll's study[49] and 3 studies reporting urine volume plus urine sodium and potassium concentrations in patients with hyperglycemia.[51–53] The highest reported average value of the sum of urinary sodium and potassium concentrations was <120 mmol/L.[51] In the 3 studies allowing calculation of urinary cation concentrations in individual patients,[51–53] all sums of urinary monovalent cation concentrations were substantially <140 mmol/L.

Large volumes of urine with monovalent cation concentration lower than normal $[Na]_S$ will increase $[Na]_S$ in accordance with the Edelman and Rose formulas. This effect of osmotic diuresis opposes the effect on $[Na]_S$ of extracellular glucose gain and can be the dominant effect in the syndrome of symptomatic nonketotic hyperglycemia, as shown below. Mean $[Na]_S$ values were in the hypernatremic range (>143 mmol/L) in the presence of markedly elevated $[Glu]_S$ in 7 studies reporting 250 episodes of nonketotic hyperglycemia.[49,54–59] In these studies, average $[Na]_S$, weighed for the number of patients in each study, was 150.2 mmol/L, whereas average weighed $[Glu]_S$ was 48.7 mmol/L (877 mg/dL). Assuming baseline values of 140 mmol/L for $[Na]_S$ and 5.6 mmol/L for $[Glu]_S$ before the development of hyperglycemia in these episodes, weighed average $[Na]_S$ at presentation with hyperglycemia should be equal to 127.6 $[=140-1.6\times(48.7-5.6)/5.6]$ mmol/L using the Katz formula, whereas the weighed average corrected $[Na]_S$ using the Al-Kudsi formula should be 162.5 $[=150.2+1.6\times(48.7-5.6)/5.6]$ mmol/L, indicating a 14% $[=(1-140/162.5)\times 100]$ weighed average deficit of body water in excess of the deficit in sodium and potassium. In the presence of severe hyperglycemia, even normal, let alone elevated, $[Na]_S$ values are associated with moderate to profound neurological manifestations of hypertonicity.[60–62]

Treatment of hyperglycemia with insulin administration reverses the hypertonicity due to extracellular glucose excess. Reversal of the hypertonicity caused by external losses of water and monovalent cations requires infusion of large volumes of hypotonic fluids.[17,22] Consequently, determination of the tonicity (the sum of sodium and potassium concentrations) of the replacement solutions requires knowledge of the parts of hypertonicity contributed by glucose excess and by excess fluid loss through osmotic diuresis.[22] The corrected value of $[Na]_S$ by the formula of Al-

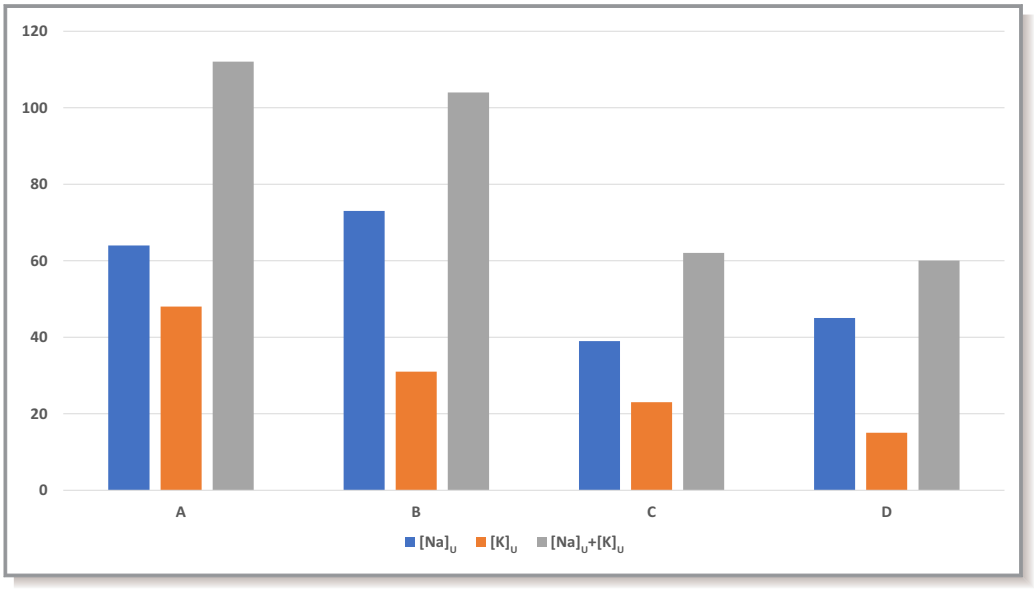

Figure 4. Average urinary sodium concentration ($[Na]_U$; in mmol/L), average urinary potassium concentration ($[K]_U$; in mmol/L), and total monovalent cation concentration in patients with glycosuric osmotic diuresis. **A**, From the study of Atchley and collaborators.[51] Note that the value of $[Na]_U$ reported by Atchley and collaborators represents an overestimate of $[Na]_U$ because this study computed the sum of urinary concentrations of sodium plus magnesium. **B**, From the study of Brodsky and coinvestigators.[52] **C**, From the study of Seldin and Tarail.[53] **D**, From the report of Arieff and Carroll.[49]

Kudsi and coauthors (formula 2 in Table 2), which is based on Katz's formula of the $\Delta[Na]_S/\Delta[Glu]_S$ ratio, has been proposed as an estimation guide of the tonicity of replacement solutions.[22] To our knowledge, the reliability of Katz's formula in patients with profound hyperglycemic osmotic diuresis has not been tested. The next section of this report presents a mathematical analysis of changes in tonicity and its determinants in hyperglycemia complicated by osmotic diuresis.

Calculation of the $\Delta[Na]_S/\Delta[Glu]_S$ Ratio and the Tonicity of Replacement Solutions in Hyperglycemia Complicated by Osmotic Diuresis

The corrected $[Na]_S$ value is used to calculate the appropriate tonicity of solutions replacing water and electrolyte losses occurring before the initiation of treatment for hyperglycemia. The volume and composition of replacement fluids used to replace losses occurring during treatment, which can be considerable, should be determined by monitoring urinary volume and monovalent cation losses.[22] The following calculations are based on the previously reported closed-system model of hyperglycemia.[30] To calculate the $\Delta[Na]_S/\Delta[Glu]_S$ ratio in an open-system model, we examined 4 schematic stages of development and correction of hyperglycemia. In each stage, we developed formulas for calculating external and internal balances of water, glucose, sodium, and potassium. Sodium salts and glucose were considered to represent the total effective extracellular solutes, and potassium salts were considered to represent the total effective intracellular solutes. The effects of the changes in these balances on tonicity and extra- and intracellular volume in each stage were the main targets of these calculations.

Four stages were studied: (1) baseline euglycemia; (2) the development of hyperglycemia without any change in external balances of water, sodium, or potassium (this stage represents a single change in extracellular solute [glucose gain]); (3) hyperglycemic osmotic diuresis, representing a combined change in body water and monovalent cations (in reality, stages 2 and 3 develop simultaneously); and (4) the correction of hyperglycemia without any further losses of water or monovalent cations (this stage represents a change in extracellular solute [loss of glucose]). Tables 2 through 5 present formulas expressing body solute and water status in stages 1 to 4. In these tables, the subscripts 1 through 4 were added to the terms of the formulas to indicate the relevant stage studied.

Table 2. Solute and Volume Expressions in the Baseline Euglycemic Stage (Stage 1)

Na_{ECF1}: $Na_{ECF1} = ECFV_1 \times [Na]_{S1}$	(6)
Glu_{ECF1}: $Glu_{ECF1} = ECFV_1 \times [Glu]_{S1}$	(7)
$Solute_{ECF1}$: $Solute_{ECF1} = ECFV_1 \times (2 \times [Na]_{S1} + [Glu]_{S1})$	(8)
$Solute_{ICF1}$: $Solute_{ICF1} = ICFV_1 \times 2 \times [K]_{ICF1} = ICFV_1 \times (2 \times [Na]_{S1} + [Glu]_{S1})$	(9)
α_1: $\alpha_1 = \frac{ICFV_1}{ECFV_1} = \frac{Solute_{ICF1}}{Solute_{ECF1}}$	(10)

$[Glu]_{S1}$ is expressed in mmol/L. Subscript numbers indicate stage. α indicates intracellular/extracellular volume ratio; ECFV, extracellular volume; Glu_{ECF}, total extracellular glucose; $[Glu]_A$, change in glucose concentration per liter of baseline extracellular volume; $[Glu]_S$, serum glucose concentration; ICFV, intracellular volume; Na_{ECF}, total extracellular sodium; $Solute_{ECF}$, total effective extracellular solute; $Solute_{ICF}$, total effective intracellular solute.

Stage 1: Baseline Euglycemia

The formulas in Table 2 express solute and volume status in stage 1, including total extracellular sodium (formula 6), total extracellular glucose (formula 7), total effective extracellular solute (formula 8), total effective intracellular solute (formula 9), and intracellular/extracellular volume ratio (α_1; formula 10).

Stage 2: Development of Hyperglycemia

Stage 2 represents a closed system, with the ratio $\Delta[Na]_S/\Delta[Glu]_S$ expressed by formula 3 in Table 1: $\Delta[Na]_{S2}=[Na]_{S2}-[Na]_{S1}$ and $\Delta[Glu]_{S2}=[Glu]_{S2}-[Glu]_{S1}$. Note that because $[Na]_{S2}$ is less than $[Na]_{S1}$, $\Delta[Na]_{S2}$ has a negative sign. In Table 3, formulas 11 through 14 express the changes from stage 1 to stage 2 in extracellular solutes and intra- and extracellular volumes, plus the intracellular/extracellular volume ratio α_2.

Figure 5 shows serum tonicity changes from stage 1 to stage 2 in patients with $[Na]_{S1}$ of 140 mmol/L, $[Glu]_{S1}$ of 5.6 mmol/L, baseline euvolemia (α_1=1.5), baseline severe hypovolemia (α_1=3.0), baseline severe hypervolemia (α_1=1.0), and rising levels of $[Glu]_A$ from 0 to 112 mmol/L. For comparable degrees of hyperglycemia, serum tonicity changes are substantially higher in hypervolemia and lower in hypovolemia than in euvolemia.

Table 3. Solute and Volume Changes During Development of Hyperglycemia in a Closed System (Stage 2)

$Solute_{GainECF2}$: $Solute_{GainECF2} = ECFV_1 \times [Glu]_{A1}$	(11)
$ECFV_2$: $ECFV_2 = TBW_1 \times \frac{Solute_{ECF1} + ECFV_1 \times [Glu]_A}{Solute_{ECF1} + ECFV_1 \times [Glu]_A + Solute_{ICF1}}$	(12)
$ICFV_2$: $ICFV_2 = TBW_1 \times \frac{Solute_{ICF1}}{Solute_{ECF1} + ECFV_1 \times [Glu]_A + Solute_{ICF1}}$	(13)
$\alpha_2 = \frac{Solute_{ICF1}}{Solute_{ECF1} + ECFV_1 \times [Glu]_A}$	(14)

$[Glu]_{A1}$ is expressed in mmol/L. Subscript numbers indicate stage. α indicates intracellular/extracellular volume ratio; ECFV, extracellular volume; $[Glu]_A$, change in glucose concentration per liter of baseline extracellular volume; ICFV, intracellular volume; $Solute_{ECF}$, total effective extracellular solute; $Solute_{GainECF}$, gain in extracellular solute (glucose); $Solute_{ICF}$, total effective intracellular solute; TBW, total body water.

Stage 3: Presentation With Hyperglycemia After Development of Osmotic Diuresis

Osmotic diuresis from hyperglycemia causes losses of body water, extracellular sodium and glucose, and intracellular potassium. Formulas 15 through 22 in Table 4 express volume and solute status in stage 3.

Figure 6 shows serum tonicity changes occurring in stage 3 in the hypothetical patients depicted in Figure 5. Tonicity values in Figure 6 were calculated using the maximal tonicity values achieved by $[Glu]_A$ of 112 mmol/L in Figure 5 and adding the rises in tonicity secondary to osmotic diuresis resulting in water loss from 0% to 25% of the baseline body water and urinary sodium plus urinary potassium concentration sums between 40 and 80 mmol/L.

Three conclusions can be deduced from Figure 6. First, the rate of rise in serum tonicity in stage 3 is determined by the fraction of body water lost through diuresis and the total monovalent cation concentration in the urine. Second, unlike the rises in tonicity as a direct result of hyperglycemia (shown in Figure 5), which do not overlap between various states of extracellular volume, rises in tonicity from hyperglycemic osmotic diuresis may overlap (Figure 6). When the degree of hyperglycemia is comparable and both the percentage loss of body water and the monovalent cation concentrations in the urine ($[Na]_U+[K]_U$) are equal in the 3 volume states, there is no overlapping of the tonicity rises between various states of extracellular volume. Under these circumstances, patients with baseline hypervolemia exhibit the highest levels and those with baseline hypovolemia exhibit the lowest levels of hypertonicity. The overlapping of the rises in tonicity is the exclusive consequence of differences in the urinary monovalent cation concentrations. In Figure 6, the lines of rise in tonicity between the baseline states of euvolemia (volume ratio α_1=1.5 at $[Na]_U+[K]_U$=40 mmol/L) and hypervolemia (α_1=1.0 at $[Na]_U+[K]_U$=80 mmol/L) intersect at the point of loss of 14% of body water and at tonicity of 371.2 mOsm/L. In the same figure, the lines of rise in tonicity between the baseline states of hypovolemia (volume ratio α_1=3.0, at $[Na]_U+[K]_U$=40 mmol/L) and euvolemia (α_1=1.5, at $[Na]_U+[K]_U$=80 mmol/L) intersect at the point of loss of 21% of body water and at tonicity of 375.7 mOsm/L. Data S1 shows the calculations of these intersection points. The third conclusion is that the rise in tonicity from pronounced osmotic diuresis is potentially higher than the corresponding rise from severe hyperglycemia.

Stage 4: Normalization of Serum Glucose Concentration Without Further External Losses of Water or Solute

The only difference between stages 3 and 4 is loss of extracellular glucose so that $[Glu]_S$ is normalized (ie, $[Glu]_{S4}=[Glu]_{S1}$): $\Delta[Na]_{S4}=[Na]_{S4}-[Na]_{S3}$ and $\Delta[Glu]_{S4}=[Glu]_{S4}-[Glu]_{S3}$. In this case, $[Glu]_{S4} < [Glu]_{S3}$; therefore, $\Delta[Glu]_{S4}$ will be negative. Formulas 23 through 27 in Table 5 express the changes in the amounts of solute and the final $[Na]_S$.

Table 4. Solute and Volume Changes Resulting From Hyperglycemic Osmotic Diuresis (Stage 3)

TBW_3: $TBW_3 = TBW_1 - V_{U3}$	(15)
Na_{ECF3}: $Na_{ECF3} = ECFV_1 \times [Na]_{S1} - V_{U3} \times [Na]_{U3}$	(16)
Glu_{ECF3}: $Glu_{ECF3} = ECFV_2 \times [Glu]_{S2}$	(17)*
$Solute_{ECF3}$: $Solute_{ECF3} = ECFV_1 \times 2 \times [Na]_{S1} - V_{U3} \times 2 \times [Na]_{U3} + ECFV_2 \times [Glu]_{S2}$	(18)
$Solute_{ICF3}$: $Solute_{ICF3} = ICFV_1 \times 2 \times [K]_{ICF1} - V_{U3} \times 2 \times [K]_{U3}$	(19)
$ECFV_3$: $ECFV_3 = (TBW_1 - V_{U3}) \times \frac{Solute_{ECF3}}{Solute_{ECF3} + Solute_{ICF3}}$	(20)
$ICFV_3$: $ICFV_3 = (TBW_1 - V_{U3}) \times \frac{Solute_{ICF3}}{Solute_{ECF3} + Solute_{ICF3}}$	(21)
α_3: $\alpha_3 = \frac{Solute_{ICF3}}{Solute_{ECF3}}$	(22)

*To demonstrate the quantitative effect of osmotic diuresis on tonicity, it was assumed that glucose loss through osmotic diuresis and glucose production were equal in stage 3, so that the amount of glucose in the extracellular compartment was equal in stages 2 and 3. Subscript numbers indicate stage. α indicates intracellular/extracellular volume ratio; ECFV, extracellular volume; Glu_{ECF}, total extracellular glucose; $[Glu]_S$, serum glucose concentration; ICFV, intracellular volume; $[K]_U$, urinary potassium concentration; Na_{ECF}, total extracellular sodium; $[Na]_S$, serum sodium concentration; $[Na]_U$, urine sodium concentration; $Solute_{ECF}$, total effective extracellular solute; $Solute_{ICF}$, total effective intracellular solute; TBW, total body water; V_U, urine volume (osmotic diuresis).

The following hypothetical example illustrates the effects of hyperglycemic osmotic diuresis on body solute and volume status.

Hypothetical Example

This example addresses a hypothetical patient with baseline body water of 40 L, extracellular volume 16 L, intracellular volume 24 L, $[Na]_{S1}$ of 140 mmol/L, and $[Glu]_{S1}$ of 5.6 mmol/L who develops hyperglycemia and osmotic diuresis. The following calculations were made, where subscript numbers indicate stage and α indicates intracellular/extracellular volume ratio; $\Delta[Glu]_S$, change in serum glucose concentration; $\Delta[Na]_S$, change in serum sodium concentration; ECFV, extracellular volume; Glu_{ECF}, total extracellular glucose; $Glu_{Removed}$, amount of glucose that should be removed; $[Glu]_A$, change in glucose concentration per liter of baseline extracellular volume; $[Glu]_S$, serum glucose concentration; ICFV, intracellular volume; $[K]_U$, urinary potassium concentration; Na_{ECF}, total extracellular sodium; $[Na]_S$, serum sodium concentration; $[Na]_{SCorrected}$, corrected serum sodium concentration; $[Na]_U$, urinary sodium concentration; $Solute_{ECF}$, total effective extracellular solute; $Solute_{GainECF}$, gain in extracellular solute (glucose); $Solute_{ICF}$, total effective

Table 5. Solute Changes During Correction of Hyperglycemia Without Any Further External Changes in Solute or Water Balance (Stage 4)

$\Delta[Glu]_{S4}$: $\Delta[Glu]_{S4} = [Glu]_{S1} - [Glu]_{S3}$	(23)
$Glu_{Removed4}$: $Glu_{Removed4} = ECFV_3 \times [Glu]_{A4}$	(24)
$[Glu]_{A4}$ as a function of $\Delta[Glu]_{S4}$: $[Glu]^2_{A4} + (\alpha_3 + 1)\times(2\times[Na]_{S3} - \Delta[Glu]_{S4}) + [Glu]_{S3}\times[Glu]_{A4} - (\alpha_3 + 1)\times\Delta[Glu]_{S4}\times(2\times[Na]_{S3} + [Glu]_{S3}) = 0$	(25)
$Solute_{ECF4}$: $Solute_{ECF4} = Solute_{ECF3} - Glu_{Removed4}$	(26)
$[Na]_{S4}$: $[Na]_{S4} = \frac{ECFV_3 \times [Na]_{S3}}{ECFV_4}$	(27)

Formula 25 was derived by rearranging formula 5 from Table 1. For $ECFV_3$ and α_3, see Table 4. $\Delta[Glu]_{S4}$, $[Glu]_{S1}$, $[Glu]_{S3}$, and $[Glu]_{A4}$ are expressed in mmol/L. Subscript numbers indicate stage. α indicates intracellular/extracellular volume ratio; $\Delta[Glu]_S$, change in serum glucose concentration; ECFV, extracellular volume; $Glu_{Removed}$, amount of glucose that should be removed; $[Glu]_A$, change in glucose concentration per liter of baseline extracellular volume; $[Glu]_S$, serum glucose concentration; $[Na]_S$, serum sodium concentration; $Solute_{ECF}$, total effective extracellular solute.

intracellular solute; TBW, total body water; Ton, tonicity; V_U, urine volume (osmotic diuresis).

Stage 1

$Ton_1=2\times140+5.6=285.6$ mOsm/L; $Na_{ECF1}=16\times140=2240$ mmol (formula 6); $Glu_{ECF1}=16\times5.6=89.6$ mmol (formula 7); $Solute_{ECF1}=2\times2240+89.6=4569.6$ mOsm (formula 8); $Solute_{ICF1}=24\times285.6=6854.4$ mOsm (formula 9); $\alpha_1=24/16=6854.4/4569.6=1.5$ (formula 10).

Stage 2

Assuming a value for $[Glu]_{A2}=112$ mmol/L of $ECFV_1$, the following calculations were made: $Solute_{GainECF2}=16\times112=1792$ mmol (formula 11); $ECFV_2=40\times(4569.6+1792)/(4569.6+1792+6854.4)=19.25$ L (formula 12); $ICFV_2=40\times6854.4/(4569.6+1792+6854.4)=20.75$ L (formula 13); $\alpha_2=20.75/19.25=6854.4/(4569.6+1792)=1.08$ (formula 14); $\Delta[Glu]_{S2}=112\times\{(1.5+1)\times140+5.6+112\}/\{(1.5+1)\times140+5.6+112)\}=92.1$ mmol/L (formula 5, Table 1); $[Glu]_{S2}=5.6+92.1=97.7$ mmol/L, or 1759 mg/dL; $\Delta[Na]_{S2}/\Delta[Glu]_{S2}=-5.6\times1.5\times2\times140/\{2\times([1.5+1]\times2\times140+5.6+112)\}=-1.44$ mmol/L per 5.6 mmol/L (formula 3, Table 1); $[Na]_{S2}=140-1.44\times92.1/5.6=116.3$ mmol/L; $Ton_2=2\times116.3+97.7=330.3$ mOsm/L; $[Na]_{SCorrected1}=116.3+1.6\times92.1/5.6=142.6$ mmol/L (formula 2, Table 1). $[Na]_{SCorrected2}=116.3+1.44\times92.1/5.6=140.1$ mmol/L (formula 4, Table 1).

Note that in the absence of any external changes in water or electrolyte balance, $[Na]_S$ should return to its baseline value of 140 mmol/L after return of $[Glu]_S$ to its baseline value of 5.6 mmol/L. Formula 4 (Table 1) calculates a corrected $[Na]_S$ value of 140.1 mmol/L essentially equal to 140 mmol/L. The error of the corrected $[Na]_S$ calculated by the formula of Al-Kudsi[26] (formula 2, Table 1), at 142.6 mmol/L, is small and has no clinical relevance in this instance.

Stage 3

Assuming an osmotic diuresis with $V_U=10$ L, $[Na]_U=45$ mmol/L, and $[K]_U=15$ mmol/L, the following calculations were made: $TBW_3=40-10=30$ L (formula 15); $Na_{ECF3}=16\times140-10\times45=1790$ mmol (formula 16); $Glu_{ECF3}=19.25\times97.7=1881.6$ mmol (formula 17); $Solute_{ECF3}=2\times1790+1881.6=5461.6$ mOsm (formula 18); $Solute_{ICF3}=6854.4-10\times2\times15=6554.4$ mOsm (formula 19); $ECFV_3=30\times5461.6/(5461.6+6554.4)=13.64$ L (formula 20); $ICFV_3=30\times6554.4/(5461.6+6554.4)$

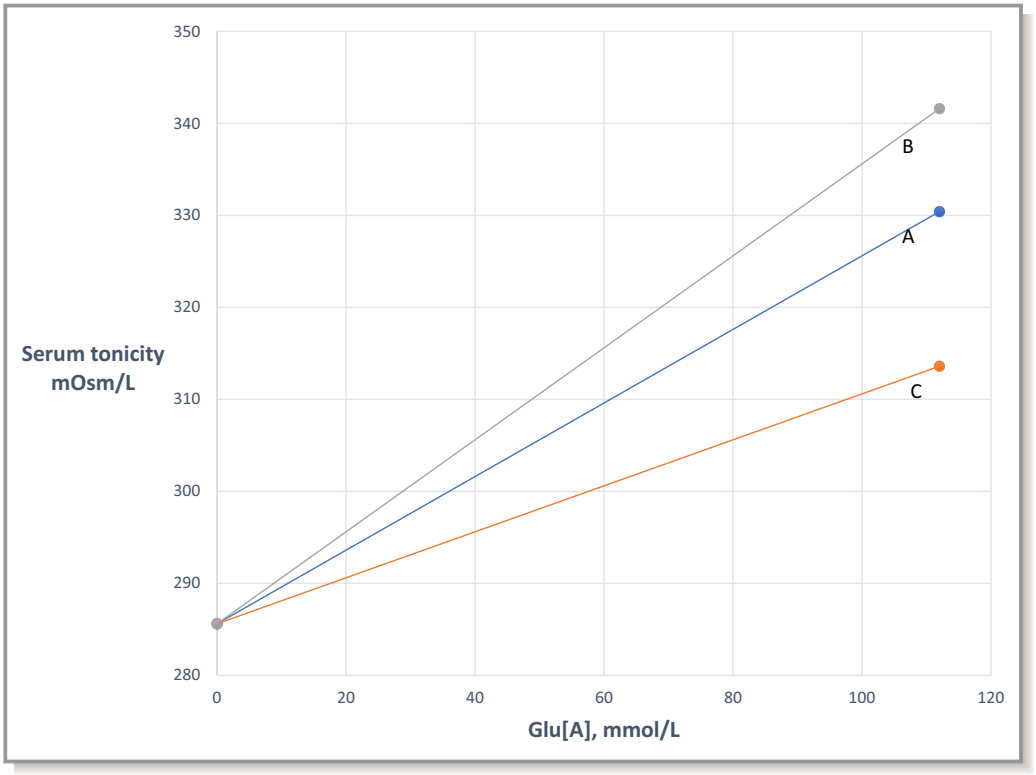

Figure 5. Increase in serum tonicity values at progressive hyperglycemia in a closed system (stage 2). Three different states of extracellular volume with the same baseline tonicity plus serum glucose and sodium concentrations are depicted. **A**, Baseline euvolemia (α_1=1.5). **B**, Baseline hypervolemia (gain of 50% in extracellular volume or euglycemic intracellular/extracellular volume ratio; α_1=1.0). **C**, Baseline hypovolemia (loss of 50% of the euvolemic extracellular volume; α_1=3.0). $[Glu]_A$ indicates change in glucose concentration per liter of baseline extracellular volume.

=16.36 L (formula 21); volume ratio α_3=16.36/13.646=1.20 (formula 22); $[Glu]_{S3}$=1881.6/13.64=137.9 mmol/L, or 2483 mg/dL; $[Na]_{S3}$=1790/13.64=131.2 mmol/L; Ton_3=2×131.2+137.9=400.3 mOsm/L.

Stage 4

For the values of $[Glu]_{S3}$, Glu_{ECF3}, $[Na]_{S3}$, $ECFV_3$, and α_3 computed in stage 3 and a desired $\Delta[Glu]_{S4}$ value of −132.3 (=5.6−137.9) mmol/L (formula 23), formula 25 takes the following form: $[Glu]_{A4}^2$+{(1.20 +1)x(2×131.2+132.3) +137.9}×$[Glu]_{A4}$+(1.20+1)×132.3x(2×131.2+137.9)=0, from which $[Glu]_{A4}$=−133.5 mmol/L. (Note: Solution of quadratic equations with the form $ax^2+bx+c=0$ is by formula $\times = \frac{-b\pm\sqrt{b^2-4ac}}{2a}$. In this case, the only acceptable solution of formula 25 is $\times = \frac{-b+\sqrt{b^2-4ac}}{2a}$. The solution $\times = \frac{-b-\sqrt{b^2-4ac}}{2a}$ produces by formula 24 ECF_3×$[Glu]_A$ values far exceeding the amount of glucose in the extracellular compartment in stage 3).

$Glu_{Removed4}$=−13.64×133.5=1820.9 mmol (formula 24); $Solute_{ECF4}$=5.461.6−1820.9=3640.7 mOsm (formula 26); $ECFV_4$=30×3640.7/(3640.7+6554.4)=10.71 L; $ICFV_4$=30×6554.4/(3640.4+6554.4)=19.29 L; α_4=19.29/10.71=1.80; $[Glu]_{S4}$=(1881.6−1820.9)/10.71=5.6 mmol/L; Ton_4=2×167.1+5.6=339.8 mOsm/L; $[Na]_{S4Corrected1}$=131.2+1.6×132.3/5.6=169.0 mmol/L (formula 2, Table 1). $[Na]_{S4Corrected2}$=131.2+132.3×1.20×131.2/ {2×(1.20+1)×2×131.2+137.9 −133.5}=167.0 mmol/L (formula 4, Table 1). Formula 27 expresses the final $[Na]_S$ at euglycemia in this stage. The corrected $[Na]_{S4}$ values derived by formulas 2 and 4 (Table 1) should be compared with the $[Na]_{S4}$ value derived from formula 27. According to formula 27, $[Na]_{S4}$=(16×140−10×15)/10.71=167.1 mmol/L. The corrected $[Na]_{S4}$ by formula 4 is almost identical to the $[Na]_{S4}$ value of 167.0 mmol/L computed by formula 27, whereas the corrected $[Na]_{S4}$ calculated by the Al-Kudsi formula (formula 2), at 169.0 mmol/L, was close to the estimates from formulas 27 and 4.

These findings suggest that the Katz $\Delta[Na]_S/\Delta[Glu]_S$ formula and the Al-Kudsi corrected $[Na]_S$ formula predict tonicity changes during correction of hyperglycemia with reasonable accuracy, even in extreme hyperglycemia and after profound osmotic diuresis. Clinical observations are needed to confirm these findings. Also note that the

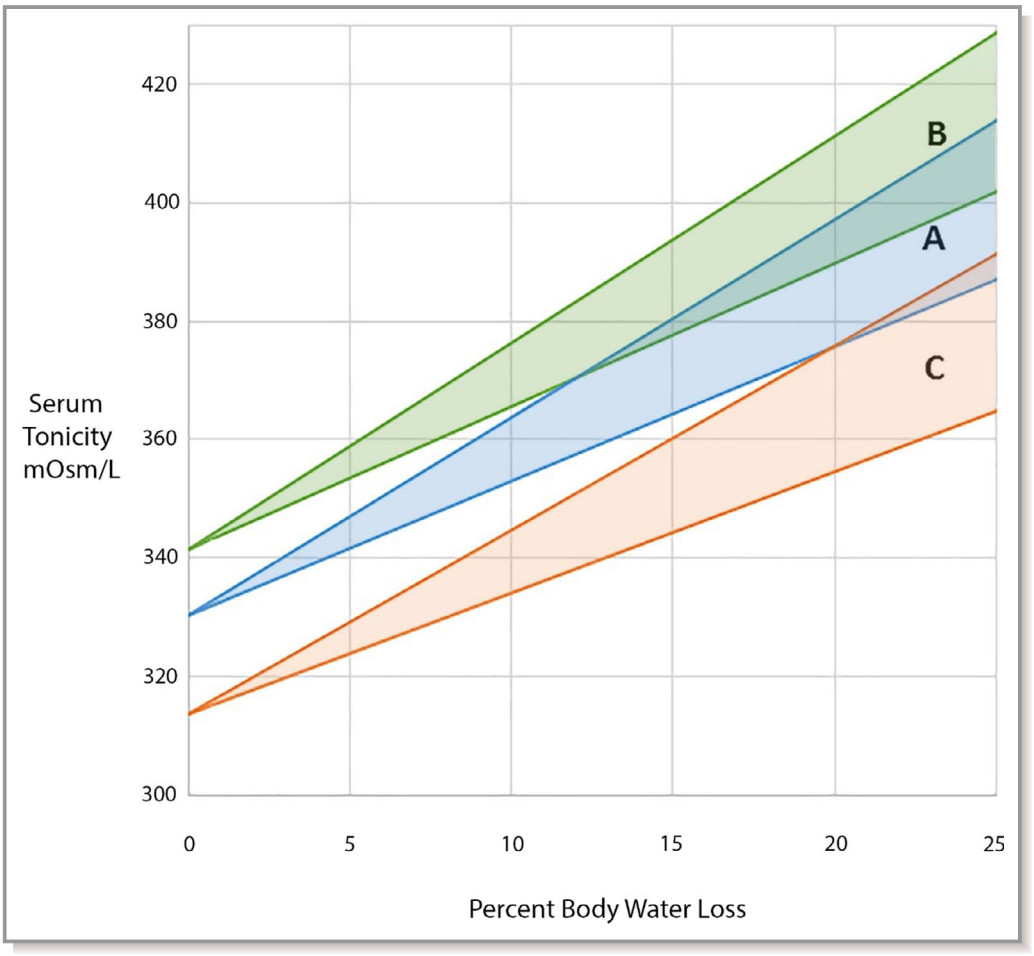

Figure 6. Increases in tonicity from osmotic diuresis in addition to the increases from development of hyperglycemia in Figure 5. **A**, Baseline euvolemia (intracellular/extracellular volume; α_1=1.5). **B**, Baseline hypervolemia (α_1=1.0). **C**, Baseline hypovolemia (α_1=3.0). The triangular areas in **A**, **B**, and **C** indicate the ranges of increase in tonicity for osmotic diuresis with urine volume varying between 0% and 25% of the baseline euglycemic body water and for the sum of urinary sodium plus potassium concentrations varying between 40 mmol/L (the lower line of each area) and 80 mmol/L (the upper line of each area).

calculations for stage 4 did not account for body fluid losses occurring during correction of hyperglycemia. Fluid and electrolyte losses through osmotic diuresis can be substantial as long as $[Glu]_S$ remains elevated. There is a critical need for monitoring these losses throughout the treatment period.

The changes in the intracellular/extracellular volume ratio in the 4 stages of this hypothetical patient reflect the corresponding changes in intracellular and extracellular volume and illustrate the clinical manifestations caused by volume changes in severe hyperglycemia. Baseline ratio in stage 1 was 1.5, total body water was 40 L, and $ECFV_1$ was 16 L. In stage 2, at $[Glu]_A$ of 112 mmol/L, the ratio was 1.08, and $ECFV_2$ was 19.25 L. Extracellular volume gained 3.25 L from stage 1 to stage 2. Gain in extracellular volume may cause the development of symptomatic circulatory overload in oligoanuric patients developing severe hyperglycemia.[24,37,63]

If the percentage loss of body water and the total monovalent cation concentration in the urine are the same in stage 3, the rise in tonicity will be the same regardless of $[Na]_U$ and $[K]_U$. However, the distribution of the water loss between the intracellular and extracellular compartments will be determined by $[Na]_U$ and $[K]_U$ as shown below. With the maximal tested value of glucose gain ($[Glu]_{A2}$=112 mmol/L) and loss of 25% of body water though osmotic diuresis with $[Na]_U$ of 45 mmol/L and $[K]_U$ of 15 mmol/L in the hypothetical patient, total body water was reduced to 30 L, the ratio α_3 was 1.20 and $ECFV_3$ was 13.64 L. $ECFV_3$ in this instance was 5.61 L lower than in stage 2 and 2.36 L lower than in stage 1. If the loss of body water (10 L) and the total monovalent cation concentration in the urine (60 mmol/L) were the same, but $[K]_U$ was 45 mmol/L while $[Na]_U$ was 15 mmol/L, the ratio α_3 would be 0.98 and $ECFV_3$ would be 15.15 (=30/1.98) L. In this instance, $ECFV_3$

would be 4.10 L lower than in stage 2 but only 0.85 L lower than in stage 1.

In stage 4, with $[Na]_U$ of 45 mmol/L and $[K]_U$ of 15 mmol/L in stage 3, the volume ratio α_4 would be 1.80 and $ECFV_4$ would be 10.71 L—2.93 L lower than in stage 3, 8.54 L lower than in stage 2, and 5.29 L lower than in stage 1. If $[Na]_U$ was 15 mmol/L and $[K]_U$ was 45 mmol/L in stage 3, the volume ratio α_4 would be 1.37 and $ECFV_4$ would be 30/2.37=12.66 L —or 2.49 L lower than in stage 3, 6.59 L lower than in stage 2, and 3.34 L lower than in stage 1. These calculations show that correction of severe hyperglycemia leads to substantial loss of extracellular volume even if there are no concomitant urinary losses of water and cations. Volume losses are compounded by ongoing osmotic diuresis during the early stage of correction. Consequently, adequate and prompt volume replacement is a dominant concern during treatment of hyperglycemic crises.[17]

Commentary

The preceding theoretical analysis and hypothetical example lead to 2 conclusions. First, estimates of the euglycemic $[Na]_S$ by the Al-Kudsi formula [26] provide a reasonable guide for the correction of hyperglycemic hypertonicity in both patients with hyperglycemia complicated by osmotic diuresis (the open system) and patients with oligoanuric hyperglycemia (the closed system), with reservations. Factors not accounted for in the Katz [25] and Al-Kudsi [26] formulas can diminish the accuracy of these formulas. In both the closed and open systems, the baseline intracellular/extracellular volume ratio is a major determinant of the changes in solute concentration during development of hyperglycemia.[30] In the open system, the magnitude of change in the volume ratio is affected by the relationship between the losses of effective intracellular solute (potassium salts) and effective extracellular solute (sodium salts) through osmotic diuresis, in addition to the extracellular gain in glucose, which is the only hyperglycemic influence on the ratio during a change in body glucose content in the closed system.

The potential of significant deviations of the final euglycemic $[Na]_S$ from Al-Kudsi's corrected value provides strong justification for close monitoring of $[Na]_S$ and $[Glu]_S$ during treatment of severe hyperglycemia. However, this formula should be used repeatedly during treatment of hyperglycemia. The corrected $[Na]_S$ is often above the normal range of $[Na]_S$ at presentation with hyperglycemia and osmotic diuresis. High corrected $[Na]_S$ values should decrease progressively during progressive decrease in $[Glu]_S$. Monitoring of the corrected $[Na]_S$ during treatment of severe hyperglycemia by the Al-Kudsi formula should guide the choice of tonicity of the replacement solutions.[22]

The second conclusion of this report is that both the volume and the composition of urine affect changes in extracellular volume in hyperglycemic crises. Extracellular volume deficits can be large at presentation with hyperglycemia[17,22,49] and are accentuated substantially if hyperglycemia is corrected without any further losses in water and monovalent cations. As shown in this report, the composition of the urine affects the magnitude of extracellular volume loss. For the same urine volume and total concentration of monovalent cations, the higher the urinary potassium concentration is, the smaller the loss of extracellular volume will be.

The calculations of this report did not account for several factors that can potentially affect the changes in the determinants of $[Na]_S$ in hyperglycemia. The first of these factors is the presence of polyanionic proteoglycan sodium stores in cartilage, bone, and primarily skin that may affect $[Na]_S$ changes in dysnatremic states.[64] Glycosaminoglycan is the main sodium-storing compound. The Rose,[10] Katz,[25] and Al-Kudsi[26] formulas and the formulas in Tables 2 through 5 do not account for sodium stored in various body tissues. Differences between $[Na]_S$ values calculated by the Rose formula [10] and by the Edelman[8] or Nguyen-Kurtz[9] formulas for the same values of body water, potassium, and sodium are substantial. The quantitative contribution of tissue sodium stores to changes in $[Na]_S$ and their effect on the accuracy of the predictive formulas during development or treatment of dysnatremias has been investigated recently.[65,66] In one study,[65] changes in $[Na]_S$ soon after termination of hypertonic saline infusion in normal volunteers were very close to the changes predicted by the Adroqué-Madias[11] and Nguyen-Kurtz[67] formulas, whereas $[Na]_S$ 4 hours after infusion decreased to a degree not explained by the urinary losses of water, sodium, and potassium in the same time period. The authors interpreted this last finding as a potential uptake of sodium by tissue proteoglycans in the face of rising $[Na]_S$. A fundamental difference between the developments of hyperglycemia and hypernatremia is that $[Na]_S$ decreases in the first and rises in the second. The role of tissue sodium stores for the change in $[Na]_S$ in hyperglycemia has not been clarified and warrants further investigation.

A second factor that can affect the accuracy of the calculations in this report is that the volumes of distribution of sodium and glucose, although "extracellular," may not be equal. Sodium volume of distribution is higher than that of other markers of extracellular volume, including bromide,[68] which is often considered the gold standard for measuring extracellular volume. Sodium ions enter the intracellular compartment. Furthermore, sodium concentration in intracellular fluids is higher in patients with several severe illnesses compared with healthy participants.[69] In contrast, Hirota and coinvestigators computed an early (3 minutes after injection) volume of distribution of glucose that was equal only to the central extracellular volume.[20] However, the apparent volume

of distribution of glucose should be higher than the extracellular volume in states characterized by insulin deficiency because insulin is not required for glucose to enter several organs with several liters of intracellular volume (eg, brain and liver).[70] The effect of differences in the apparent volumes of distribution of sodium and glucose on the osmotic consequences of development and correction of hyperglycemia, including the formulas predicting $\Delta[Na]_S/\Delta[Glu]_S$, is another area requiring further research.

A final factor affecting the calculations in this report is the differences in the concentrations of sodium and glucose between plasma or serum and interstitial fluid. Sodium concentration differences between the 2 compartments are due to 2 factors. One is the expression of $[Na]_S$ as sodium concentration per serum volume even though sodium is present only in the water component of the serum; this leads to underestimation of sodium concentration in serum water by 7% when the water fraction of serum is 0.93.[9] The second factor is the presence in the serum of polyanions, which attract cations according to the Gibbs–Donnan equilibrium. The traditional Gibbs–Donnan coefficient for calculating interstitial sodium concentration from $[Na]_S$ is equal to 0.95; for example, if $[Na]_S$ is 140 mmol/L, the interstitial sodium concentration is 143 ($=140\times0.95/0.93$) mmol/L. In patients with hemoconcentration from large losses of extracellular fluid, as in hyperglycemic syndromes, both coefficients for calculating interstitial sodium concentration from $[Na]_S$ should change. The magnitude of these changes and their effect on the relationship between $[Na]_S$ and interstitial sodium concentration will vary depending on the degree of hemoconcentration. In addition, elevated plasma protein concentration from hemoconcentration and/or hyperlipidemia in hyperglycemia may cause spuriously low measurement of $[Na]_S$ by indirect potentiometry or flame photometry.[71] Interstitial glucose concentration should be higher than $[Glu]_S$ by 7% at normal serum water fraction or by a higher percentage in conditions causing hemoconcentration. In contrast, mean interstitial glucose concentration was assumed to be lower than $[Glu]_S$ when there was cellular uptake of glucose[72] (eg, during treatment of hyperglycemic crises with insulin). The differences between total extracellular sodium and glucose and their values calculated assuming equal concentrations in the intravascular and interstitial compartments also require further investigations.

The quantitative contributions on the changes in $[Na]_S$ of sodium stores, any differences between the apparent volumes of distribution of glucose and sodium, and the differences between the serum and interstitial concentrations of glucose and sodium could be the sources of substantial errors in the calculation of the composition of the replacement solutions for hyperglycemic crises. Calculation of the volume of replacement solutions for losses due to osmotic diuresis before the start of treatment presents even greater difficulties, which are addressed in detail elsewhere.[22,73] Finally, losses of water and electrolytes during treatment through ongoing osmotic diuresis and other organ systems, including the gastrointestinal tract, the respiratory system, and the skin, are unpredictable. Great caution is required when treating severe hyperglycemic episodes. These treatments should be carried out in intensive care units. Volume deficits require prompt replacement with infusion of saline.[17] The optimal rate of infusion is best decided by continuous monitoring of the vital signs. The tonicity (the total monovalent cation concentration) of the infusions should be decided by monitoring the corrected $[Na]_S$ by the Katz and Al-Kudsi formulas,[22] which may provide erroneous estimates in some instances, as noted. The rate of volume infusion and the potassium replacement and tonicity of the infusate should be determined and adjusted as informed by close monitoring of the patient's clinical status, serum potassium, $[Na]_S$, $[Glu]_S$, corrected $[Na]_S$, urine volume, and, in some instances, urinary sodium and potassium concentrations. Monitoring these items is a critical component of the management of hyperglycemic crises.[22]

Disclosures

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Key Words: hyperglycemia • hypovolemia • osmotic diuresis • potassium balance • sodium balance • tonicity

SUPPLEMENTAL MATERIAL

Data S1.

Appendix

Calculation of the percent of body water loss at which the rising tonicities of the baseline extracellular volume states shown in Figure 6 intersect

This Appendix shows the calculation of the degree of body water loss (fraction of body water β) that is required for serum tonicities to become equal if $[Na]_U$ plus $[K]_U$ is 40 mmol/L in the state with the lower overall rate of rise in tonicity (State A) and 80 mmol/L in the state with the higher overall rate of rise in serum tonicity (State B). For these calculations, it was assumed that intracellular volume (ICFV) is the same (1.5 L) at baseline euvolemia in all three extracellular volume (ECFV) states depicted in Figures 5 and 6. Therefore, in baseline euvolemia (α_1 = 1.5) ECFV = 1 L and baseline total body water (TBW_1) = 2.5 L, in baseline hypervolemia (α_1 = 1.0) ECFV = 1.5 L and TBW_1 = 3.0 L, and in baseline hypovolemia (α_1 = 3.0) ECFV = 0.5 L, and TBW_1 = 2.0 L. Note that so long as the initial relationships ICFV/ECFV (α_1) are the same the calculations shown below will provide the same results regardless of the individual sizes of ICFV and ECFV.

A. Comparison of baseline euvolemia (α_1 = 1.5) and baseline hypervolemia (α_1 = 1.0):

State A (α_1 = 1.5)

Tonicity at stage 2, before the start of osmotic diuresis (Ton_2) = 330.4 mOsm/L.

A. Body solute at stage 2 = 2.5×330.4 = 826 mOsm.
B. Body water lost at the intersection of tonicities point = 2.5×β L.
C. Total body water at the intersection of tonicities point = 2.5 – 2.5×β L.

D. Solute lost in the urine ($[Na]_U + [K]_U$ = 40 mmol/L) at the intersection of tonicities point = $2\times40\times2.5\times\beta = 200\times\beta$ mOsm.

E. Body solute at the intersection of tonicities point = $826 - 200\times\beta$ mOsm.

F. Tonicity at the intersection of tonicities point = $(826 - 200\times\beta)/(2.5 - 2.5\times\beta)$ mOsm/L.

State B ($\alpha_1 = 1.0$)

Ton_2 = 341.6 mOsm/L.

A. Body solute at stage 2 = $3.0\times341.6 = 1024.8$ mOsm.

B. Body water lost = $3.0\times\beta$ L

C. Total body water = $3.0 - 3.0\times\beta$ L.

D. Solute lost ($[Na]_U + [K]_U$ = 80 mmol/L) = $2\times80\times3.0\times\beta = 480\times\beta$ mOsm.

E. Body solute at intersection of tonicities = $1024.8 - 480\times\beta$ mOsm.

F. Tonicity at the intersection point = $(1024.8 - 480\times\beta)/(3.0 - 3.0\times\beta)$ mOsm/L.

Tonicities calculated by E formulas) in states A and B are equal. Therefore:

G. $(826 - 200\times\beta)/(2.5 - 2.5\times\beta) = (1024.8 - 480\times\beta)/(3.05 - 3.0\times\beta)$.

The acceptable solution of the quadratic relation expressed in formula G is $\beta = 0.14$. Entering of 0.14 for β in formulas E reveals a tonicity value of 371.2 mOsm/L for both state A and state B.

B. Comparison of baseline hypovolemia ($\alpha_1 = 3.0$) and baseline euvolemia ($\alpha_1 = 1.5$):

State A ($\alpha_1 = 3.0$)

Ton_2 = 313.6 mOsm/L.

A. Body solute at stage 2 = $2.0\times313.6 = 627.2$ mOsm.

B. Body water lost = 2.0×β L.

C. Total body water = 2.0 – 2.0×β L.

D. Solute lost ($[Na]_U + [K]_U$ = 40 mmol/L) =2×40×2.0×β = 160×β mOsm.

E. Body solute at intersection of tonicities = 627.2 - 160×β mOsm.

F. Tonicity at the intersection point: = (627.2 - 160×β)/(2.0 –2.0×β) mOsm/L.

State B (α_1 = 1.5)

Ton_2 = 330.4 mOsm/L.

A. Body solute at stage 2 = 2.5×330.4 = 826 mOsm.

B. Body water lost = 2.5×β L.

C. Total body water = 2.5 – 2.5×β L.

D. Solute lost ($[Na]_U + [K]_U$ = 80 mmol/L) = 2×80×2.5×β = 400×β mOsm.

E. Body solute at intersection of tonicities = 826 - 400×β mOsm.

F. Tonicity at the intersection point: = (826 - 400×β)/(2.5 –2.5×β) mOsm/L.

G. (627.2 - 160×β)/(2.0 – 2.0×β) = (826 - 400×β)/(2.5 –2.5×β).

The acceptable solution of the quadratic relation expressed in formula G is β = 0.21. Entering 0.21 for β in formulas E reveals a tonicity value of 375.7 mOsm/L for both state A and state B.